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Original Communications

AGE AND AURICULAR FIBRILLATION AS INDEPENDENT FACTORS IN AURICULAR MURAL THROMBUS FORMATION

WILLIAM E. HAY, M.D., AND SAMUEL A. LEVINE, M.D.
BOSTON, MASS.

AURICULAR mural thrombi have been found in most forms of heart disease, and are known to be particularly common in rheumatic heart disease. That their presence or absence has a marked bearing on the span of life cannot be denied. Weiss and Davis[1] have shown that rheumatic heart disease, more than any other form, is responsible for embolic manifestations. In this kind of heart disease there are several possible factors that play a part in their formation, i.e., the duration of the rheumatic heart disease, the presence of congestive failure and its duration, the presence of mitral stenosis, auricular fibrillation, persistent rheumatic inflammatory activity within the heart, and age.

Levine and Harvey,[2] in a study of uninfected mural thrombi, selected a group of thirty-one cases in which there was definite evidence of auricular fibrillation, with the idea of showing the effect of auricular fibrillation on the site of thrombus formation. Ninety per cent of those patients had auricular mural thrombi. In comparing them with eighty patients who had regular rhythm and mural thrombi, they found that only 54 per cent of the latter had thrombi in the auricles. Weiss and Davis,[1] in a study of 164 cases of rheumatic heart disease, selected 131 cases in which the rhythm had been accurately ascertained. There were seventy-four patients, or 57 per cent, who had persistent auricular fibrillation, paroxysmal fibrillation, or flutter. They found that 88 per cent of those with extensive auricular thrombi had auricular fibrillation. Graef, et al.,[3] in reviewing 178 cases of rheumatic heart disease, found twenty-four, or 13 per cent, in which there were auricular thrombi. They concluded that certain conditions favored the development of auricular thrombi in rheumatic heart disease, among which were severe

From the Medical Clinic of the Peter Bent Brigham Hospital and the Department of Medicine, Harvard Medical School, Boston.
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mitral stenosis, congestive heart failure, auricular fibrillation, and continued local inflammation. Likewise Garvin,[4] in a study of 116 cases of rheumatic heart disease, found that mural thrombi were more common among the patients with auricular fibrillation (43.3 per cent) than among those with regular rhythm (18 per cent). He also has shown that in rheumatic heart disease mural thrombi are more common in the older patients.

All of the above investigators were of the opinion that auricular fibrillation plays a part in the formation of auricular mural thrombi. Inasmuch as it will be shown below that patients with rheumatic heart disease with fibrillation are distinctly older than those with regular rhythm, it is clear that all of the above studies need to be reconsidered with due control of the age factor. The important question is whether patients of the same age, with similar valve lesions, will have a different incidence of mural thrombi, depending on whether auricular fibrillation is present or not. As far as is known, this type of analysis has not previously been made. Is there an age factor at all, and, if there is, is it large or small?

TABLE I

	NO. OF CASES	NO. REGULAR RHYTHM	AV. AGE REGULAR	THROMBI WITH REGULAR RHYTHM	NO. OF CASES OF AURICULAR FIBRILLATION	AV. AGE AURICULAR FIBRILLATION	THROMBI WITH AURICULAR FIBRILLATION
Under 40 years	75	45	25.9	4 (8.8%)	30	26.7	10 (33.3%)
Over 40 years	111	35	55.3	7 (20.0%)	76	53.2	42 (55.2%)
Total	186	80	38.7	11 (13.8%)	106	45.7	52 (49.0%)

A study was therefore conducted of the post-mortem records of the Peter Bent Brigham Hospital in all cases of mitral stenosis, with or without other valvular disease (cases of bacterial endocarditis were excluded). The data for the following analysis are summarized in Table I. There were 186 cases, in 106 of which, or 57.1 per cent, auricular fibrillation was present. Regular rhythm was present in eighty, or 42.9 per cent. The average age at death of the patients with regular rhythm was 38.7 years, whereas, in the group with auricular fibrillation, the average age at death was 45.7 years. In the group with regular rhythm there were eighty patients, and eleven, or 13.8 per cent, had mural thrombi. In the group with auricular fibrillation there were 106 cases, in fifty-two, or 49 per cent, of which, mural thrombi were present. The above analysis confirms what other authors have shown, i.e., that mural thrombi are much more common in fibrillators than in patients with regular rhythm. But it also shows that the former are, on the average, seven years older than the latter, and therefore had a longer time for the development of mural thrombosis.

In order to ascertain the part that age played in the formation of mural thrombi, it was necessary to divide the patients into two groups, namely, those 40 years of age and over, and those under 40 years of age. In the group 40 years of age or over, the average age at death in the cases of regular rhythm was 55.3 years. In those of auricular fibrillation the average age at death was 53.2 years. These two groups are now comparable as far as age is concerned, and differ only in cardiac rhythm. There were thirty-five patients with regular rhythm who were 40 or more years of age, and seven, or 20 per cent, had mural thrombi. In the similar group with auricular fibrillation there were seventy-six cases, in forty-two, or 55.2 per cent, of which, mural thrombi were present. From this analysis it follows that auricular fibrillation was conducive to the development of auricular mural thrombi entirely independent of the age factor.

In the group under 40 years of age it was found that the average age at death of those with regular rhythm was 25.9 years, and in those with auricular fibrillation it was 26.7 years. In the group with regular rhythm there were forty-five cases, in four (8.8 per cent) of which mural thrombi were present. In the group with auricular fibrillation there were thirty cases, in ten, or 33.3 per cent, of which, mural thrombi were found. Here again it is clear that mural thrombi were four times as frequent in the fibrillators as in those with regular rhythm, although the ages were the same.

The role that age plays as a factor independent of the presence or absence of auricular fibrillation is well indicated by comparing the occurrence of thrombi in the older and younger groups. Amongst those over 40 years of age the incidence of mural thrombi in the fibrillators was 55.2 per cent, and, in those with regular rhythm, it was 20 per cent, whereas in the two corresponding groups of patients under 40 years of age the incidence was 33.3 per cent and 8.8 per cent, respectively. It follows that younger patients, whether the cardiac rhythm is regular or irregular, are less prone to mural thrombosis.

CONCLUSIONS

An analysis was made of 186 cases of mitral stenosis in order to ascertain the respective roles that age and auricular fibrillation play in the production of auricular mural thrombosis. It was found that both the advancing age of the patient and the presence of auricular fibrillation independently increase the incidence of auricular mural thrombosis in cases of mitral stenosis.

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FACTORS INFLUENCING IMMEDIATE MORTALITY AFTER ACUTE CORONARY OCCLUSION

ROBERT M. WOODS, M.D., AND ARLIE R. BARNES, M.D.
ROCHESTER, MINN.

THE problem of prognosis after acute coronary occlusion was given its now accepted and universally recognized significance by Herrick,[1] in 1912, when he showed that acute coronary obstruction is not necessarily immediately fatal. Herrick predicted at that time that patients who had mild forms of the disease and patients who had gained complete functional recovery probably would be encountered. The advance of knowledge of the principles and the practical application of electrocardiography since that time have greatly facilitated the diagnosis of acute coronary occlusion, as well as the cardiac irregularities which may arise subsequent to acute coronary occlusion.

Various authors have written concerning the factors which may influence the prognosis after acute coronary occlusion. Wiggers[2] was of the opinion that the two most important are the onset of ventricular fibrillation and the onset of failure of the left side of the heart. Blumer[3] observed that embolism originating in mural thrombi occurred among 14 per cent of the patients who had myocardial infarcts. Willius[4] showed that the previous occurrence of coronary occlusion makes the prognosis more grave than it would be if the condition were initial. Brill[5] believed that an atypical electrocardiogram is an unfavorable prognostic sign. Strong[6] stated that low blood pressure and particularly low pulse pressure make the prognosis ominous.

NATURE OF PRESENT STUDY

Purpose.—It is the purpose of this paper to evaluate the factors which are present in, or arise subsequent to, acute coronary occlusion, and lead to death either during the acute attack itself or during the first six weeks after the occurrence of the occlusion.

Material.—One hundred twenty-eight unselected patients with acute coronary occlusion who were under our observation were chosen for this study. There are included in this study persons who died very suddenly, either while they were engaged in normal activity or while they were convalescing from some surgical procedure. In such cases a positive diagnosis of acute coronary occlusion was made on the evidence

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From the Mayo Clinic, Rochester.

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found at necropsy. Of these 128 patients, sixty-eight survived the acute attack and were still living at the time of this report. The remaining sixty patients died within six weeks after the onset of the acute attack. In the entire series there were 108 males and twenty females, a ratio of 5.4 to 1.

GENERAL CONSIDERATIONS

Incidence of Immediate Mortality.—The incidence of immediate mortality in the respective age groups is shown in Fig. 1 and Table I. The average age for all the patients in the entire series was 55 years; the average age of the patients who lived was 51.3 years, as compared with an average age of 59.2 years for those who died within the immediate period.

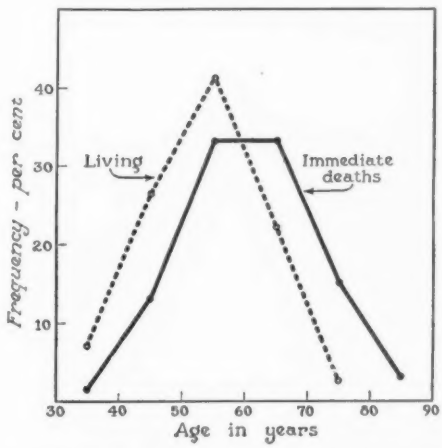

Fig. 1.—The distribution according to age in each series of cases of acute coronary occlusion. The group of living patients includes sixty-eight patients, and the group of immediate deaths includes sixty patients.

TABLE I

INCIDENCE OF IMMEDIATE MORTALITY IN RESPECTIVE AGE GROUPS

AGE (YEARS)	CASES	IMMEDIATE DEATHS	
		NO.	%
Less than 50	32	9	28.1
50 to 59	48	20	41.7
60 to 69	35	20	57.1
70 and more	13	11	84.6
Total	128	60	46.9

TABLE II

INCIDENCE OF IMMEDIATE MORTALITY ACCORDING TO SEX IN TWO MAIN AGE GROUPS

AGE (YEARS)	MEN			WOMEN		
	CASES	IMMEDIATE DEATHS		CASES	IMMEDIATE DEATHS	
		NO.	%		NO.	%
Less than 60	73	25	34.2	7	4	57.1
60 and more	35	20	57.1	13	11	84.6
Total	108	45	41.7	20	15	75

In Table II is shown the incidence of immediate mortality, computed according to sex in the two main groups: patients who were 60 years old or less, and those 61 years old or more.

Relationship of Previous Attacks of Coronary Occlusion.—Fig. 2 shows the relationship of previous coronary artery disease to the outcome in both series of cases.

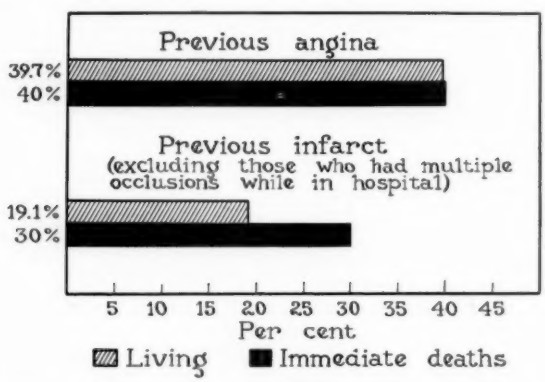

Fig. 2.—Incidence of previous disease of the coronary artery in both series of patients with acute coronary occlusion; that is, those who survived the immediate period after the acute attack, and those who died.

The Effects of Infarction.—In Table III the incidence of the position of the infarct in the respective groups is shown. The position of the infarct was ascertained by examination of the hearts at necropsy, or, in the case of those who survived, was inferred from the electrocardiographic changes when they were sufficiently characteristic to permit localization.

TABLE III

INCIDENCE OF POSITION OF INFARCT (AS LOCALIZED BY THE ELECTROCARDIOGRAM AND SEEN AT NECROPSY)

POSITION OF INFARCT	LIVING AND DEAD		LIVING		IMMEDIATE DEATHS	
	NO.	%	NO.	%	NO.	%
Anterior	62	48.4	36	52.9	26	43.3
Posterior	52	40.6	30	44.1	22	36.7
Unlocalized	11	8.5	2	3	9	15
Multiple	3	2.5			3	5
Total	128	100	68	100	60	100

In an effort to ascertain the influence which the position of the infarct had on the outcome, the patients were grouped as shown in Fig. 3. Of the sixty-two patients with anterior apical infarction, 42 per cent died within the immediate period and the remaining 58 per cent survived the acute coronary occlusion. Of the fifty-two patients with posterior basal infarction, 42 per cent died within the immediate period and the remaining 58 per cent survived the acute coronary occlusion. Of the eleven patients who had an infarct which could not be localized by electrocardio-

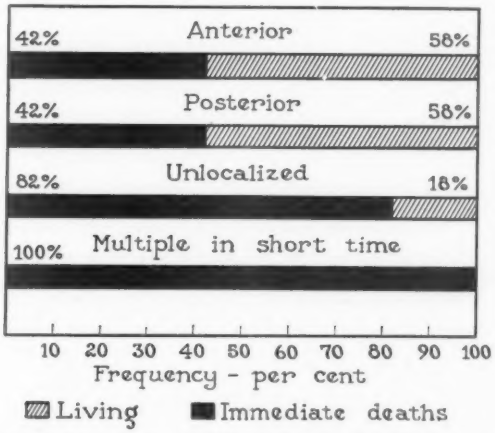

Fig. 3.—The relationship of the position of the infarct to the ultimate outcome. There were sixty-two anterior infarcts, fifty-two posterior infarcts, and eleven unlocalized infarcts. Moreover, three other patients had multiple infarcts within a short period.

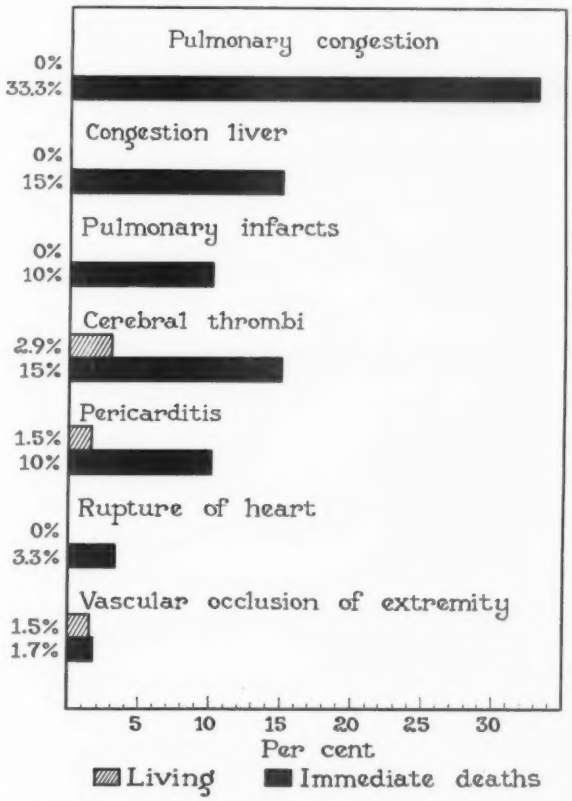

Fig. 4.—Relative incidence of the important complications among both groups of patients; that is, those who survived the immediate period of the acute attack of coronary occlusion, and those who died. These complications all occurred within the first six weeks (immediate period) after onset of the acute attack of coronary occlusion.

graphic evidence, 82 per cent died within the immediate period and the remaining 18 per cent survived. Three of the 128 patients had multiple occlusions while they were under observation in the hospital, and all three died within the immediate period.

Complications After Coronary Occlusion.—Complications which arise secondary to acute coronary occlusion influence to a great extent the immediate prognosis. Fig. 4 shows the relative frequency of the important complications in each series of cases.

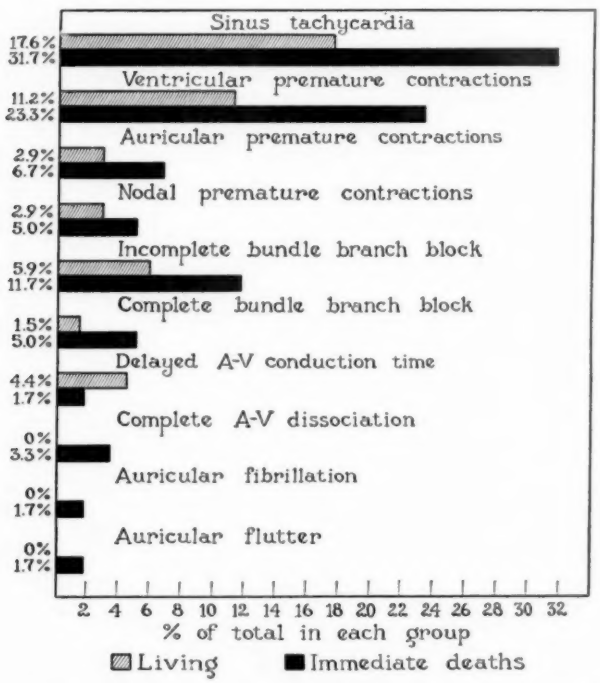

Fig. 5.—Incidence of various cardiac irregularities, as demonstrated in the electrocardiograms of patients in both groups in this series of cases of acute coronary occlusion. None of these cardiac irregularities was known to have been present in any case prior to the acute attack of coronary occlusion.

Cardiac Irregularities.—Whenever possible, electrocardiographic tracings were made at intervals, in an effort to observe changes which would have diagnostic significance and also to help demonstrate any cardiac irregularities which might have developed subsequent to the coronary occlusion and acute myocardial infarction. Fig. 5 shows graphically the incidence of the various cardiac irregularities in each group of this series of patients. The significance of the sinus tachycardia which occurred in nineteen of the patients who died in the immediate period is emphasized by the fact that, ultimately, nine of these nineteen patients developed myocardial decompensation from which they never recovered; in eight of the remaining ten patients, progressively serious cardiac

irregularity developed, and it was assumed that the terminal condition was ventricular fibrillation; the remaining two patients died of pulmonary embolism.

TABLE IV

RELATIONSHIP OF VENTRICULAR EXTRASYSTOLES TO IMMEDIATE DEATHS

FREQUENCY OF EXTRASYSTOLES	NO. OF CASES	LIVING %	DEAD %
Occasional (1 in 21 cardiac beats)	3	100	0
Moderately frequent (1 in 11 to 1 in 20 cardiac beats)	3	100	0
Very frequent (1 in 2 to 1 in 10 cardiac beats)	17	17.6	82.4

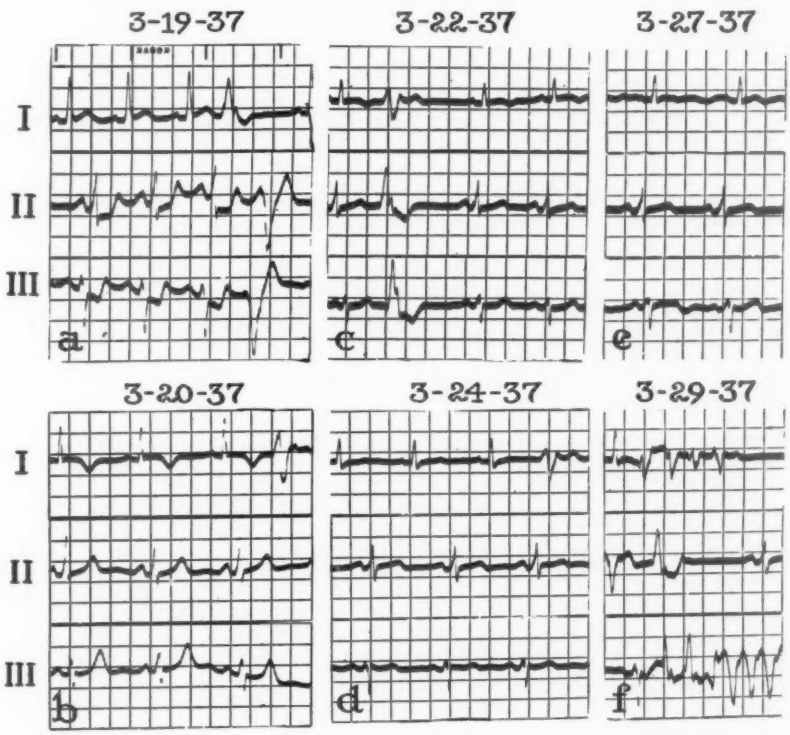

Fig. 6.—*a*, Electrocardiogram made several days after the patient had had an acute attack of coronary occlusion; there was one ventricular extrasystole in every four beats on March 19, 1937; *b*, on March 20, 1937, there was only one ventricular extrasystole in the entire record; *c*, on March 22, 1937, the ventricular extrasystoles became more frequent (once in every five beats); *d*, on March 24, 1937, the ventricular extrasystoles became still more frequent (once in every four beats); *e*, on March 27, 1937, none of the ventricular extrasystoles seen in the previous tracings were visible; *f*, on March 29, 1937, there were frequent series of varying lengths of consecutive ventricular extrasystoles. This patient died March 30, 1937.

Judging from the work of Fishberg,[7] Fromet,[8] Mahaim,[9] Lisa,[10] and many other observers, we may assume that the occurrence of ventricular extrasystoles after acute coronary occlusion is an ominous sign. Ventricular extrasystoles were demonstrated electrocardiographically in 11.2

per cent of the patients who lived, and in 23.3 per cent of the patients who died within the immediate period. In an effort to ascertain further the significance of these ventricular extrasystoles, their relative frequency was studied. Table IV gives the results. Ventricular premature contractions were considered to be "occasional" if they occurred only once in every twenty-one beats, or more. Ventricular premature contractions of occasional frequency developed in three patients, and all survived. Ventricular premature contractions were considered to be of "moderate" frequency if they occurred between once in every twenty beats and once in every eleven beats. Ventricular premature contractions of moderate frequency developed in three patients, and none of them died. Ventricular premature contractions were considered to be "very frequent" if they occurred between once in every ten beats and once in every two beats. Ventricular premature contractions which were considered to be very frequent developed among seventeen patients. Fourteen of these patients (82.4 per cent) died and three (17.6 per cent) survived.

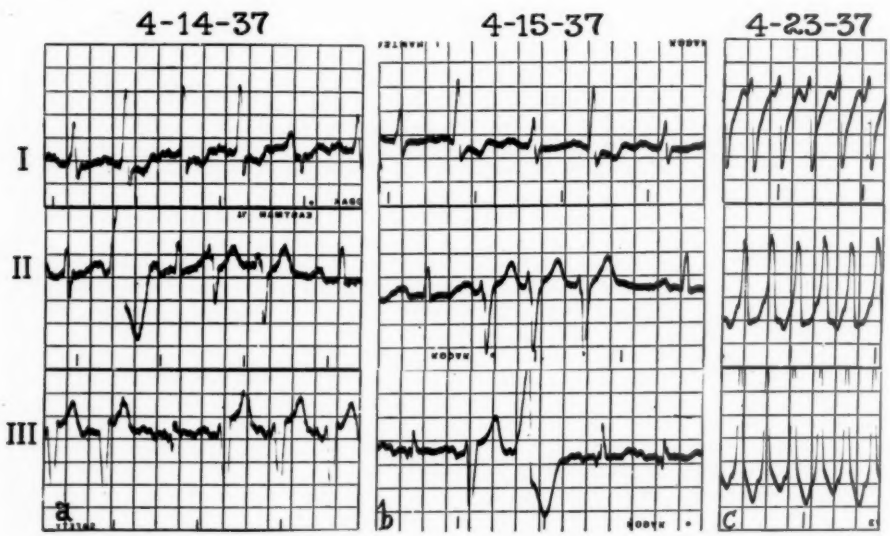

Fig. 7.—Series of electrocardiograms made at varying intervals after an acute attack of coronary occlusion; *a*, on April 14, 1937, several days after the acute attack had occurred, the normal beats were followed by a series of four or five ventricular extrasystoles from multiple foci; *b*, on April 15, 1937, one ventricular extrasystole occurred for each normal beat, as well as frequent short series of ventricular extrasystoles from multiple foci; *c*, on April 23, 1937, several hours before the death of the patient, ventricular tachycardia was present, with a rate of 254 beats per minute.

Fig. 6*a*, *b*, *c*, *d*, *e*, and *f* is a series of electrocardiograms which were made after acute coronary occlusion in one of the cases in this series. The one (Fig. 6*a*) made March 19, 1937, revealed one ventricular extrasystole in every four beats, slight elevation of the S-T segment in Lead I, and a depressed S-T segment in Leads II and III. In the tracing (Fig. 6*b*) made on the next day, definite inversion of the T wave in Lead I

appeared, but only one ventricular extrasystole was visible in the entire record. The electrocardiogram (Fig. 6*c*) made March 22, 1937, showed that the ventricular extrasystoles had become very frequent again; they were occurring once in every five beats. The ventricular extrasystoles were still frequent on March 24 (Fig. 6*d*), but were completely absent in the tracing (Fig. 6*e*) made March 27, 1937. Frequent extrasystoles and short runs of ventricular tachycardia were present in the tracing (Fig. 6*f*) made March 29, 1937. The patient died March 30, 1937, possibly from ventricular fibrillation.

Fig. 7*a*, *b*, and *c* shows the electrocardiograms which were made on another of the patients who died after an acute attack of coronary occlusion. The first tracing (Fig. 7*a*) was made April 14, 1937, several days after the cardiac accident had occurred, and it shows that one normal beat was followed by a series of four or five ventricular extrasystoles which arose from multiple foci. The next day (Fig. 7*b*) there was one ventricular extrasystole for every normal beat, as well as frequent, short series of extrasystoles originating from multiple foci. The electrocardiogram (Fig. 7*c*) made April 27, 1937, several hours before this patient died, revealed that the very frequent ventricular extrasystoles which had been present previously had led to ventricular tachycardia, with a rate of 254 beats per minute. It is possible that ventricular fibrillation supervened and caused the patient's death.

PATHOLOGIC DATA

Since the object of this paper is, as previously stated, to evaluate the factors which influence immediate mortality after acute coronary occlusion it was deemed advisable to ascertain the type of pathologic process and the manner in which death occurred in each of the sixty patients who died within the immediate period. Post-mortem examination of forty-eight of these sixty patients was carried out, and, in the case of the remaining twelve who died, all of the factors which were present were considered in an effort to ascertain the exact sequence of the pathologic events which caused death. It is to be stressed, first, that every patient in this group of sixty had acute coronary occlusion. Table V shows the observations which were made in this particular part of the study. Thirteen of the sixty patients died during the acute attack. These patients had very definite acute coronary artery occlusion, and some of them also had acute myocardial infarction. Three of these thirteen patients had had an attack of coronary occlusion several days before and died while they were suffering from a second attack. Since nothing else was found at necropsy to account for death, and since these patients died during an acute attack, it seems necessary to assume that some abnormality of the cardiac rhythm was the cause. In the light of the previous evidence, we believe that this abnormal cardiac mechanism was ventricular fibrillation. In nineteen other patients nothing

was found at necropsy except acute coronary occlusion and acute myocardial infarction. Clinically, however, nine of these patients had exhibited very frequent ventricular premature contractions, and these had become progressively more frequent until ventricular tachycardia developed among some of them. It is logical to suspect that frequent ventricular extrasystoles, ventricular tachycardia, and ventricular fibrillation are likely to be sequential phenomena under these circumstances. It is difficult to explain the cause of the deaths of the remaining ten of these nineteen patients, unless some serious cardiac arrhythmia is assumed to have been present, such as ventricular fibrillation of the type described by Wiggers.

TABLE V

PROBABLE CAUSES OF DEATH IN 60 CASES OF ACUTE CORONARY OCCLUSION

Death during the acute attack (ventricular fibrillation?)	13
Death after the acute attack (ventricular fibrillation?)	19
Myocardial decompensation with gradual failure:	
Pulmonary congestion	10
Pulmonary and hepatic congestion	5
Cerebral thrombosis	4
Massive fatal pulmonary embolism	6
Rupture of the heart with cardiac tamponade	2
Complete auriculoventricular dissociation	1

Evidence of cardiac enlargement in a patient suffering from acute coronary occlusion is believed to be an unfavorable prognostic sign. Necropsy revealed definite enlargement of forty-five of the forty-eight hearts which were examined. At the time of necropsy the estimated average normal weight of the forty-eight hearts was calculated to be 330 Gm.; actually, their average weight was 496 Gm. One heart weighed 720 Gm., and only three weighed less than the estimated normal.

Fifteen of the sixty patients who died within the immediate period gave definite evidence, both clinically and pathologically, of severe myocardial failure after the onset of the acute coronary occlusion and myocardial infarction. Ten of these patients had marked pulmonary congestion (Table V). Examination at necropsy revealed marked chronic passive congestion of the lungs. The other five patients displayed both clinical and pathologic evidence of pulmonary and hepatic congestion (Table V). In addition to the pulmonary observations, it was noted clinically that there was rapid and progressive hepatic enlargement, which, at necropsy, was revealed to be extensive, acute (and, in some cases, chronic) passive congestion of the liver. The average weight of the livers of these five patients was 2,400 Gm., as compared with the average normal of 1,800 Gm. These five patients also had extensive degrees of infarction of the interventricular septum.

Cerebral thrombosis, after which the patient failed rapidly, was present in four instances and was considered to be the cause of death in each of these cases (Table V).

Massive pulmonary embolism, with extensive pulmonary infarction, was noted, and considered to be the cause of death, in six of the sixty patients who died within the immediate period (Table V). Interestingly enough, the site of the thrombus from which the pulmonary emboli originated was not the heart, but one or both iliac vessels.

Rupture of the heart, with cardiac tamponade, was demonstrated at necropsy in two patients (Table V).

One patient had complete auriculoventricular dissociation, and he died during an Adams-Stokes attack which occurred within the immediate period after the acute coronary occlusion.

COMMENT

Of the factors which influence the immediate mortality after acute coronary occlusion, age is the most important. The incidence of acute coronary occlusion in this series was greatest among patients who were 55 years old. However, although 62.5 per cent of the 128 patients in this series had had acute coronary occlusion before the age of 60 years, the incidence of immediate mortality in this group was only 36.2 per cent. The remaining 37.5 per cent of the patients had acute coronary occlusion after they had reached the age of 60 years, and the incidence of immediate mortality in this particular group was 64.5 per cent. It is readily seen that the immediate mortality rate is approximately twice as high among patients who are attacked by acute coronary occlusion after the age of 60 years as it is among those who are attacked before the age of 60 years.

Males in this series predominated by a ratio of 5.4 to 1, but the incidence of immediate mortality for the males was only 41.7 per cent, as contrasted to that of 75 per cent for the females (Table II). This is explained by the fact that 65 per cent of the females in the series were 60 years of age or older, whereas only 32.5 per cent of the males in the entire series were 60 years old or more.

Another of the important factors which influence the immediate mortality rate is the onset of myocardial failure after acute coronary occlusion (Table V).

Evidence is presented to suggest that ventricular fibrillation, either immediate or delayed, probably is another important factor which influences immediate mortality after acute coronary occlusion. Wiggers[2] has shown that ventricular fibrillation may occur immediately during an acute attack of coronary occlusion, or its appearance may be delayed for a period of several days or weeks. Levy[11] has shown that attacks of ventricular fibrillation, terminating in death, have been observed frequently, and Robinson and Bredeck[12] have added that, once the ventricles fibrillate, they rarely recover normal rhythm. Fromet[8] has shown that ventricular tachycardia is the link which connects ventricular extrasystoles with ventricular fibrillation. Numerous other observers, among whom are Lisa, MacWilliam, and Mahaim,[13] are of the opinion that an

acutely damaged myocardium is hyperirritable, and that the infarcted portions may be the foci of ectopic beats which, by their summation, lead to ventricular fibrillation. There are certain observations which lead us to assume that this sequence of events occurred in a number of the cases in the present series. In thirteen cases sudden cardiac death occurred during the acute attack itself. Such deaths are difficult to explain, except as the result of a disturbance of rhythm, such as ventricular fibrillation. Nineteen other patients who died within the immediate period may have died of ventricular fibrillation which was delayed in onset. Nine of these patients had electrocardiographic evidence of very frequent ventricular extrasystoles, which then recurred with increasing frequency. In one case a long period of ventricular tachycardia occurred, and the patient died a short time later. It is possible that short periods of ventricular tachycardia might have been found among the remaining eight patients if electrocardiograms had been made at more frequent intervals.

These observations lead us to believe that ventricular fibrillation is foreshadowed by a certain sequence of events. Specifically, our observations suggest that ventricular extrasystoles, when frequent, are very likely to be followed by ventricular tachycardia, and not infrequently by ventricular fibrillation.

Massive pulmonary embolism was the immediate cause of death in 10 per cent of all the patients in this series who died within the immediate period. The source of these pulmonary emboli was not the heart, but the iliac vessels. The convalescent period which follows acute coronary occlusion is ideal for the formation of iliac thrombi because of the decrease in blood pressure after the acute attack and the complete rest in bed and inactivity of the patient.

Using the electrocardiogram to localize the position of the infarct, we found that the incidence of immediate mortality when anterior apical and posterior basal infarcts are present was exactly the same, but the incidence of immediate mortality in the cases in which the position of the infarct could not be localized was twice as high as it was in the cases in which the electrocardiogram clearly indicated the location of the infarct.

SUMMARY AND CONCLUSIONS

One hundred twenty-eight patients who had acute coronary occlusion were studied in an attempt to ascertain the factors which caused sixty of the 128 patients to die within a period of six weeks, while the remaining sixty-eight patients survived the immediate period.

The average age of all the patients in this series was 55 years, and the average age of the patients who survived was 51.3 years, as compared with an average age of 59.2 years for those patients who died within the immediate period. The incidence of immediate mortality among those patients who had acute coronary occlusion after the age of

60 years was approximately twice as high as that among the patients who had acute coronary occlusion before the age of 60 years.

In this series the males predominated by a ratio of 5.4 to 1, but the incidence of immediate mortality among the males was only 41.7 per cent, as compared with an incidence of immediate mortality of 75 per cent among the females. This is explained by the fact that most men who have acute coronary occlusion have it before the age of 60 years, whereas most women who are afflicted by acute coronary occlusion have it after the age of 60 years. The incidence of immediate mortality among those patients who had anterior apical infarcts and those who had posterior basal infarcts was exactly the same, 42 per cent. If it was not possible, however, to localize the position of the infarct by the electrocardiographic pattern which it produced, the incidence of immediate mortality was considerably higher, namely, 81.8 per cent.

The appearance of ventricular extrasystoles after acute coronary occlusion is an unfavorable sign, for these ectopic beats, if they occur very often, apparently have a tendency to increase in frequency until ventricular tachycardia is produced, and this may be followed, in turn, by ventricular fibrillation and death. Once they occur after an acute attack of coronary occlusion, these ventricular extrasystoles must be considered as ominous signs, for, although they may fluctuate and may not be seen in the electrocardiogram at times, nevertheless they do reappear with even greater frequency than before, and within a short time may lead to ventricular tachycardia. Electrocardiograms of this sequence of events are presented. Among nine patients in this series, ventricular extrasystoles which became manifest after an acute attack of coronary occlusion had been very frequent at the onset, and in one patient (Fig. 7) these ventricular extrasystoles then recurred with increasing frequency until they precipitated ventricular tachycardia. It is suggested that in such cases ventricular fibrillation may have ultimately caused death, although its actual existence was never demonstrated.

Rapid and progressive myocardial failure immediately followed acute coronary occlusion and caused death within the immediate period in fifteen of the sixty cases. When a large septal infarct is present, as was encountered in five of these fifteen patients, myocardial failure becomes manifest within a relatively short period and progresses very rapidly.

Massive pulmonary emboli occurred among six of the sixty patients who died within the immediate period.

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SKIN TEMPERATURE CHANGES CAUSED BY SMOKING AND OTHER SYMPATHOMIMETIC STIMULI

J. H. WEATHERBY, PH.D.
RICHMOND, VA.

WITHIN relatively recent years there has accumulated an extensive literature concerning the effects of tobacco on the circulatory system. Generally, such phenomena as changes in blood pressure, pulse rate, and the behavior of peripheral blood vessels, as indicated by changes in the temperature of the skin of the extremities, have been taken as qualitative and quantitative criteria of the nature of these effects. Agreement among the various investigators is by no means perfect, particularly with respect to changes in skin temperature. Also, many investigators seem to have overlooked certain physical and physiologic factors in the production of skin temperature changes which may be of crucial importance in so far as they concern interpretation of these changes. The purpose of this investigation is threefold: first, to add further information, either in confirmation of, or in contradiction to, that already reported; second, to report observations not previously mentioned in the literature; and, third, to interpret these data as carefully as possible, with due consideration for the physical and physiologic environment in which the experiments were conducted. Most of the very extensive bibliography on the subject is omitted for the purpose of conserving space.

THE PROBLEM

After observing changes in the temperature of the skin of the extremities, particularly of the magnitude often reported for the toes (occasionally as much as 6° to 7° C.), it is not surprising that deleterious changes in tissues should be ascribed to them. Does not a single cigarette cause vasoconstriction which persists for almost an hour? And if a person smokes at intervals of forty-five minutes or an hour, would not the peripheral vessels remain in a constricted condition throughout virtually the entire waking period? If this is true, how can the tissues of the hands and feet escape injury such as is seen in thromboangiitis obliterans? Here, as in any other examples of inductive reasoning, the truth and accuracy of the conclusion obviously depend on the truth and accuracy of the premises on which it is based. In this connection it may be well to ask several additional questions. Are the conditions

From the Department of Physiology and Pharmacology, Medical College of Virginia, Richmond.
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under which temperature measurements are made in the laboratory or hospital comparable to those which exist while the subject is engaged in his usual, daily activities? If vasoconstriction occurs routinely after smoking, is it sufficiently intense to interfere seriously with vital processes in the tissues involved? Are people in general subject to other vasoconstrictor influences which are comparable in frequency and magnitude to smoking? The proper evaluation of the vasoconstriction produced by smoking as an etiologic or influencing factor in peripheral vascular diseases must depend in a large measure on the answers to these questions. Also, the value of skin temperature measurements as a diagnostic aid, and in following the course of such diseases, depends on a full understanding of the factors involved in the regulation of the temperature of the skin of the extremities.

It is obvious that the conditions under which one lives and does his habitual smoking are not comparable to those which generally exist when skin temperature studies are being made in the laboratory. Some investigators, recognizing the necessity for controlling all factors and conditions as completely as possible, have conducted their experiments during the morning hours, with their subjects in the basal metabolic state. This practice assures greater uniformity in the metabolic activities of their various subjects, but it must be admitted that in the ordinary course of events the frequency with which anybody smokes with his body in the basal state is exceedingly limited.

Practically no information has been found in the literature concerning the question whether or not the intensity of the vasoconstriction, as indicated by a fall in temperature, is sufficient to interfere with normal processes in the tissues involved. This question, among others, appears to be answered, at least in part, by experiments to be described later.

The third question, concerning other vasoconstrictor influences to which people in general are subjected during the ordinary course of events, has already been answered in part. Smithwick[1] reports a decrease in blood flow through the finger after a deep breath, immersion of the contralateral hand in cold water, a loud noise, or an unpleasant thought. Similar results are reported by Finesinger, Heusner, and Smithwick.[2] Mulinos and Shulman[3] observed a decrease in skin temperature after a deep breath, such as the inhalation of tobacco smoke, and state that the vasoconstriction is exaggerated by an irritating or painful stimulus which may accompany or shortly follow the deep breath. Also, many investigators comment on the necessity of maintaining quiet during the course of the temperature measurements in order that unnecessarily great fluctuations in temperature may be avoided. Although these various types of stimuli undoubtedly produce peripheral vasoconstriction and a fall in the skin temperature of the extremities, apparently few authors, in reporting such phenomena, have made a direct comparison between the extent of the constriction which they produce and that caused by smoking. In the final analysis, these various

stimuli can be considered comparable to smoking only if the magnitudes of the several effects are comparable also. Observations on this phase of the problem will be presented.

EXPERIMENTAL ENVIRONMENT AND SUBJECTS

It is obvious that, if a fall in the temperature of the skin is to be obtained, the initial temperature of the skin must be higher than that of the surrounding atmosphere. In this connection it should be noted that, in the event of complete vasoconstriction, the temperature of the fingers and toes may fall one or two degrees below that of the surrounding atmosphere as a result of evaporation of moisture from the surface of the skin. The extent of this additional fall below atmospheric temperature depends on the secretion of sweat and the rapidity with which it evaporates.

Standard environmental conditions closely approximating those selected by Sheard, Roth, and Horton[4] (25° C. and 40 per cent relative humidity) were found to be satisfactory for most of the experiments reported here. At temperatures of about 22° C. or less, spontaneous vasoconstriction usually occurs in normal subjects who are lightly covered and in a resting state. Consequently, the actual temperature differential between the skin and the atmosphere may be less at the lower room temperature, rather than greater, because of the lower initial skin temperature. Under these conditions, further vasoconstriction, e.g., from smoking, cannot produce as great a fall in temperature as is frequently observed when the room temperature is higher, and skin temperature higher in proportion. At atmospheric temperatures of about 28° C. or higher, active vasodilatation occurs in the vessels of the toes, and in the fingers at slightly lower temperatures, as pointed out by Sheard, Roth, and Horton.[4] Consequently, at these higher room temperatures vasoconstriction must operate in antagonism to the dilator influence of heat. Further, higher atmospheric temperatures reduce the differential between skin and atmosphere so that the extent of the potential fall with vasoconstriction is again reduced. The author has repeatedly observed that, at a room temperature of 25° to 26° C., most subjects have toe temperatures of 30° to 33° C. and finger temperatures of 32° to 34° C., although occasionally under these conditions (particularly in the morning hours) toe temperatures were only a degree or two above room temperature. In fact, skin temperatures of less than 27° C. occurred spontaneously so often during the morning hours, even among subjects who had not smoked since the preceding day, that experimentation for the most part was limited to the afternoon hours. Low skin temperatures during the morning hours were observed to be especially frequent among women subjects, four of whom rarely smoked. Sudden noises and interruptions during the course of the experiments were reduced as much as possible, although not always eliminated entirely.

The group of subjects for these experiments consisted of eight women and sixteen men. Four of the women and two of the men were non-smokers. All were normal, healthy persons whose ages varied between 24 and 40 years. With one exception, all were medical students, instructors, or other laboratory workers, so that their participation as subjects probably gave rise to minimum psychic changes. Generally, about four experiments were performed on each subject, although as many as eight or ten were performed on several.

All subjects were comfortably clothed, with only the face, feet, hands, and one arm exposed. With women subjects the regular clothing was supplemented with a blanket over the legs to decrease heat loss from their bare surfaces. Each subject lay on a cot for twenty to thirty minutes before the beginning of observations, or until the temperature of the fingers and toes became relatively constant at a level above 30° C. All refrained from smoking for one or two hours before the experiment. Longer periods of abstinence did not seem to alter the results materially. As a matter of fact, skin temperatures in the morning, eight to ten hours after the last smoke, frequently were lower than those in the afternoon, only one hour after the last smoke. Skin temperatures were measured by means of a thermopile attached to a suitable galvanometer.* These measurements were made at five-minute intervals on the dorsal and palmar surfaces of the third finger near the distal end, and on the dorsal and plantar surfaces of the great toe. Simultaneous records of systolic and diastolic blood pressures and pulse rates were made. In many of the experiments on male subjects, kymographic records of respiratory movements were made during the entire period of observation by means of apparatus similar to that described by Greene and Coggeshall.[5]

EXPERIMENTAL RESULTS

Effects of Smoking.—Under the conditions described above, the smoking of a cigarette (with inhalation) by one accustomed to their use results in the following changes: the systolic blood pressure is elevated 10 to 25 mm. Hg in most subjects, although occasionally, in those who appear to be hypersusceptible, it may be more; the diastolic blood pressure is increased to approximately the same extent, although in some instances the increase is greater in proportion, which results in a decreased pulse pressure; the pulse rate is increased 5 to 20 beats per minute, although again in the hypersusceptible subject the increase may be as much as 30 beats per minute, or even more; the skin temperature of the finger drops 2° to 5° C.; and the skin temperature of the toe drops 3° to 7° C. These changes persist for various periods of time in different subjects, and in the same subject at different times. Usually the time required for recovery is roughly proportional to the magnitude of the change, and varies from fifteen minutes to as much as forty or

*Tycos Dermatherm, manufactured by the Taylor Instrument Co.

fifty minutes, or occasionally even longer. Essentially the same changes were observed in women as in men. These results are in substantial agreement with many of those reported in the literature.

The effects of tobacco on non-users were found to be much less marked than on habitual users. Apparently this is because nonsmokers do not inhale the smoke, as a rule, and consequently absorb less of the active constituents of the smoke. The circulatory system and the skin often show slight changes of the sort observed in habitual smokers, but not infrequently the skin, particularly of the fingers, shows an increase in temperature rather than a fall. In the single experiment in which a nonsmoker practiced inhalation, the changes in the circulatory system and skin temperature were of the same order of magnitude and in the same direction as those observed among habitual smokers. In addition to this, the subject experienced considerable nausea.

Degree and Duration of Vasoconstriction.—The question of greatest importance to be asked as a result of these studies is not whether vasoconstriction does or does not occur, but whether the vasoconstriction which has been observed directly as well as indirectly by many investigators is of sufficient intensity and duration to deprive the tissues of the minimal amount of blood necessary for their proper function. A direct answer to this is not forthcoming at the present time, partly because minimal requirements in terms of cubic centimeters per minute have not been established. However, evidence bearing directly on this question has been obtained in the following manner. Sheard, Horton, and Williams[6] found that, if vasoconstriction is complete, so that no heat is being brought to the fingers and toes as warm blood, then Newton's law of cooling may be applied, and the coefficient of cooling (or warming) may be calculated from the following equation:

$$T_t = T_o\, e^{-at} \text{ which may be written } a = \frac{1}{t} \log_e \frac{T_o}{T_t}$$

in which T_o is the initial difference in temperature between environment and the tissue; T_t is the difference in temperature at any specified time t; and a is a constant or coefficient of cooling or warming as the case may be. That is to say, a represents the fraction by which the magnitude of the change in temperature during any period is decreased below that of the period immediately preceding. From the more than eighty temperature curves which were obtained in this study, those from the subjects who showed the most precipitate drop in temperature, regardless of cause, were selected. It cannot be stated with certainty that in these instances the blood vessels were completely constricted, with no blood flowing through them, but it is reasonable to suppose that they represent more nearly complete vasoconstriction than any others in the group. Theoretical cooling curves were then constructed by applying the equation shown above to those parts of actual temperature curves which

showed the greatest rates of change in temperature. It is interesting that neither theoretical curve is based on a temperature change after smoking, but after some other form of stimulation. Fig. 1 shows such theoretical cooling curves, constructed from data obtained from the palmar surface of the finger and the plantar surface of the toe of one

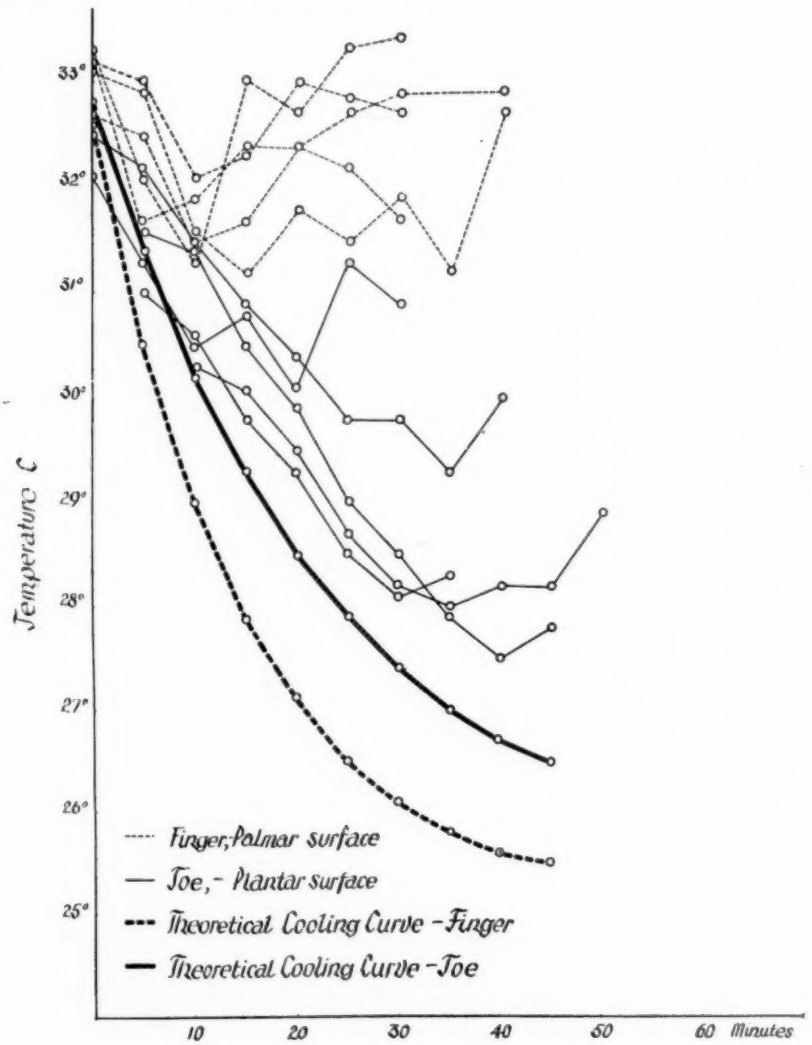

Fig. 1.

subject, as well as actual temperature curves for the same surfaces after smoking cigarettes. It follows, then, that any curve constructed from observed temperatures which does not show a rate of cooling as great as the maximum indicates that vasoconstriction was not complete, and that blood was still flowing through the tissues, although at a reduced

rate. Comparison of the actual temperature curves with the theoretical curves indicates that maximal vasoconstriction may not occur at all, or that it may occur with a duration of ten to thirty-five minutes. Then the flow of blood through the tissues is re-established, or increased if it had never been shut off completely, and the temperature curve follows a course appreciably above that of the theoretical curve for that person.

Effect of High Atmospheric Temperature on Vasoconstriction After Smoking.—Since environmental temperatures of 28° C., or higher, were found by Sheard, Roth, and Horton[4] to cause active vasodilatation, the question arises whether or not this dilatation is sufficient to overcome the constrictor influence of smoking. Several experiments were performed with this question in mind. The room temperature was increased to 29°-30° C. The temperature of the extremities under these conditions was increased to 34°-35° C. for the fingers, and 33°-34° C. for the toes. This provided a temperature differential of 4° to 6°, to which may be added an additional degree or two because of the cooling effect of the evaporation of moisture from the surface of the skin. That is to say, in the event of complete vasoconstriction, the temperature of the skin could have been decreased by as much as 6° or 7°. Actually, under these conditions, the temperature of the finger fell only about one-half degree, and that of the great toe, less than one and one-half degrees, after smoking. Within ten to fifteen minutes after cessation of smoking the temperature of both finger and toe was back to the presmoking level. A second cigarette, forty-five minutes after the first, caused no greater change than the first. This experiment was performed on two habitual smokers, each of whom consistently shows a fall of four or five degrees or more when room temperature is maintained at 25° C. It is evident, therefore, that the positive vasodilator stimulus provided by a room temperature of 29° to 30° C. was sufficient to inhibit almost completely the vasoconstrictor influence of smoking. Systolic and diastolic blood pressures and pulse rates were elevated to approximately the same extent as in other experiments on the same subjects at the lower room temperature.

Effect of Smoking on the Rate of Warming.—That smoking provides a relatively weak vasomotor stimulus is indicated further by the following experiments on three male subjects. The room temperature was maintained at 29° to 30° C., as in the previous experiments. The subjects immersed their feet in water at 15° C. for a period of five minutes. Beginning five minutes after removal of the feet from the cold bath, temperature observations were made at five-minute intervals at several places on the surface of the feet. This was repeated, so that two groups of control observations were obtained on each subject. From this it was found that ten to thirty minutes were required for the skin temperature to regain its normal level under these conditions. The experiment was repeated again, except that the subject began smoking a cigarette about

two minutes after removal of the feet from the cold bath. Under the influence of smoking (with inhalation), approximately one hour was required for the temperature of the feet to regain the normal level in two of the subjects. The third subject in this group did not inhale, as did the others, with the result that normal temperature levels were re-established within twenty minutes. However, the ingestion of 175 c.c. of cold water (15° C.) by this third subject immediately after removal of the feet from the cold bath resulted in such a decrease in rate of warming that thirty minutes were required for re-establishment of normal temperature levels (control period, ten minutes for this subject).

Effect of Removal of Nicotine.—Several experiments were performed in which the subject smoked so-called "denicotinized" cigarettes of a brand available commercially. The effects on skin temperature and circulatory system were not significantly different from those obtained with ordinary cigarettes. The subject used in these experiments is considered to be a hyper-reactor, at least with respect to tobacco. This lack of a significant difference may be explained in at least two ways: first, the changes usually observed after smoking an ordinary cigarette are not caused by nicotine, but by some other constituent; and second, that although nicotine is the agent responsible, maximal effects may be produced by quantities far less than those contained in ordinary brands, and that there still remains in the so-called "denicotinized" brand sufficient nicotine to produce approximately maximal effects. Analyses of the brand used indicate a nicotine content of a little less than 1 per cent.

In order to evaluate the role of nicotine in the production of the characteristic changes in circulation and skin temperature after smoking, the nicotine was removed completely from cigarettes of a popular brand by subjecting them to steam distillation for a period of eight hours. The addition of a small amount of ammonia to the steam apparently resulted in the quantitative replacement of nicotine in the tobacco by ammonia, so that the final acid-base balance of the cigarette was not materially altered. Chemical analyses indicated that the nicotine content was so low as to be practically undetectable. To some of these nicotine-free cigarettes the original nicotine content was restored by injecting a solution of nicotine acetate from a hypodermic syringe. This was done by inserting a long needle through the end of the cigarette and depositing 0.01 c.c. of solution of the proper concentration at intervals of 5 mm.

The effects on blood pressure, pulse rate, and skin temperature of smoking one of these nicotine-free cigarettes (with inhalation) by an habitual smoker were similar in most respects to the effects of an ordinary cigarette when the smoke was *not inhaled;* that is, the blood pressure and pulse rate showed no significant change, and the skin temperature fell only a degree, or slightly more, at most. Occasionally the

skin temperature, particularly of the fingers, was elevated instead of depressed. On the other hand, smoking a renicotinized cigarette by an habitual smoker (with inhalation) produced changes like those produced by the original cigarette (Fig. 2). It is difficult to estimate whether or not the effects of the renicotinized cigarette were quantitatively the same as those of the normal, untreated cigarette, for each subject shows considerable variation in his responses from day to day. However, in these subjects, the effects of the renicotinized cigarette were within the range of variability previously observed for each subject. The marked difference between the effects produced by the nicotine-free cigarette and that to which the nicotine had been restored indicates that the changes in blood pressure, pulse rate, and temperature of the skin of the extremities are caused, for the most part, by the nicotine contained in the latter, and not by altered respiratory movements associated with smoking, as suggested by Mulinos and Shulman.[3]

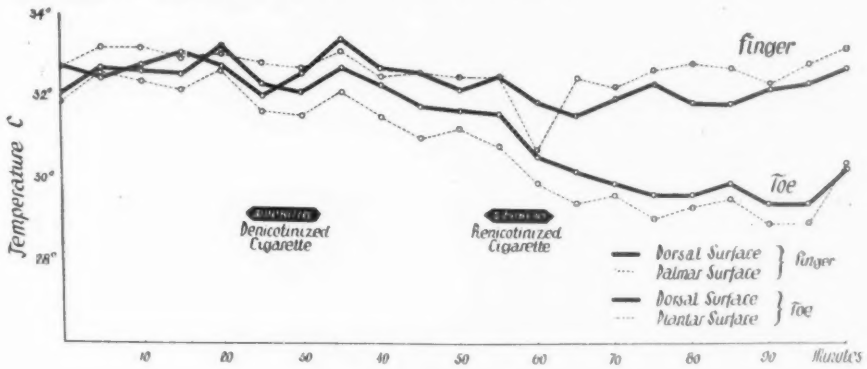

Fig. 2.

Effect of Altered Respiratory Movements During Smoking.—Further evidence that the altered respiratory movements associated with smoking were of relatively little importance in bringing about the fall in skin temperature was obtained from kymographic records of the respiration of many subjects (both smokers and nonsmokers) before, during, and after smoking. The changes appeared to be quite inconsistent. In some nonsmokers, respiratory exchange seemed somewhat depressed during smoking. Some habitual smokers showed relatively slight irregularity during the smoking period, as compared with the pre- and post-smoking periods, whereas others showed considerable irregularity, particularly as a result of inhalation. Of special significance is the fact that two subjects who consistently showed nearly equal temperature changes also showed the greatest differences in respiratory records; one was quite regular, and the other was quite irregular.

Effects of Other Physiologic and Psychic Stimuli.—At frequent intervals throughout the course of the experiments on smoking it was observed that sudden changes in skin temperature occurred, even before

the subject had begun smoking. These changes often were associated with such incidents as the ringing of the telephone, the opening of a door, or other minor disturbances. Such observations, along with those previously reported in the literature, prompted the investigation of the effects of several physiologic and psychic stimuli on skin temperature. These were hyperventilation, the drinking of cold water, a sudden noise, reading, and talking. The hyperventilation consisted of breathing at approximately twice the normal depth for a period of one minute. Usually about ten such breaths were taken during the course of one minute. The cold water was at a temperature of about 12° C., and each subject drank about 150 to 175 c.c. Sudden noises were produced by crushing an inflated paper bag, dropping the lid upon a metal box, or slamming a door. Apparently, any form of reading matter, science or fiction, served equally well, and pictures were found to have a similar effect. Conversation, regardless of subject, was generally effective, although subjects of immediate or personal interest produced greater effects. All these types of stimuli caused a significant fall in skin temperature of a magnitude which often approached or even exceeded that observed after smoking (Fig. 3). Occasionally there was what appeared to be a spontaneous fall in temperature which could not be associated with any known stimulus. The magnitude of the changes brought about by these different activities varied between wide extremes, which makes an arithmetic average fall in temperature, or an average increase in systolic blood pressure or pulse rate, of questionable significance. The important feature in this connection is that every habitual smoker, with the possible exception of two hypersusceptible subjects, exhibited changes after one or more of these physiologic or psychic stimuli which often were as great as those observed after smoking.

Additive Effects.—Not infrequently it was observed that the effects of one stimulus were superimposed on those of another which had occurred earlier, as mentioned by Mulinos and Shulman.[3] As an example, occasionally the telephone rang, or someone entered the laboratory shortly after the temperature curve after smoking had reached a minimum level and had begun to ascend, resulting in a resumption of the downward trend of the curve (Fig. 3).

Effect of Smoking on the Active Subject.—All the experiments described above were performed on subjects who were lying down, with their feet and hands exposed, and provide little information which can be applied to those who are wearing the usual foot coverings and are moving about performing their routine duties. For the purpose of obtaining information about temperature changes under the more normal conditions, an iron-constantan thermocouple was sewed into the toe of a sock in such a position that it was in contact with the skin of the plantar surface of the great toe. The shoe was then replaced. The thermocouple was attached to a recording thermometer* by means of

*Celectray, manufactured by the C. J. Tagliabue Co.

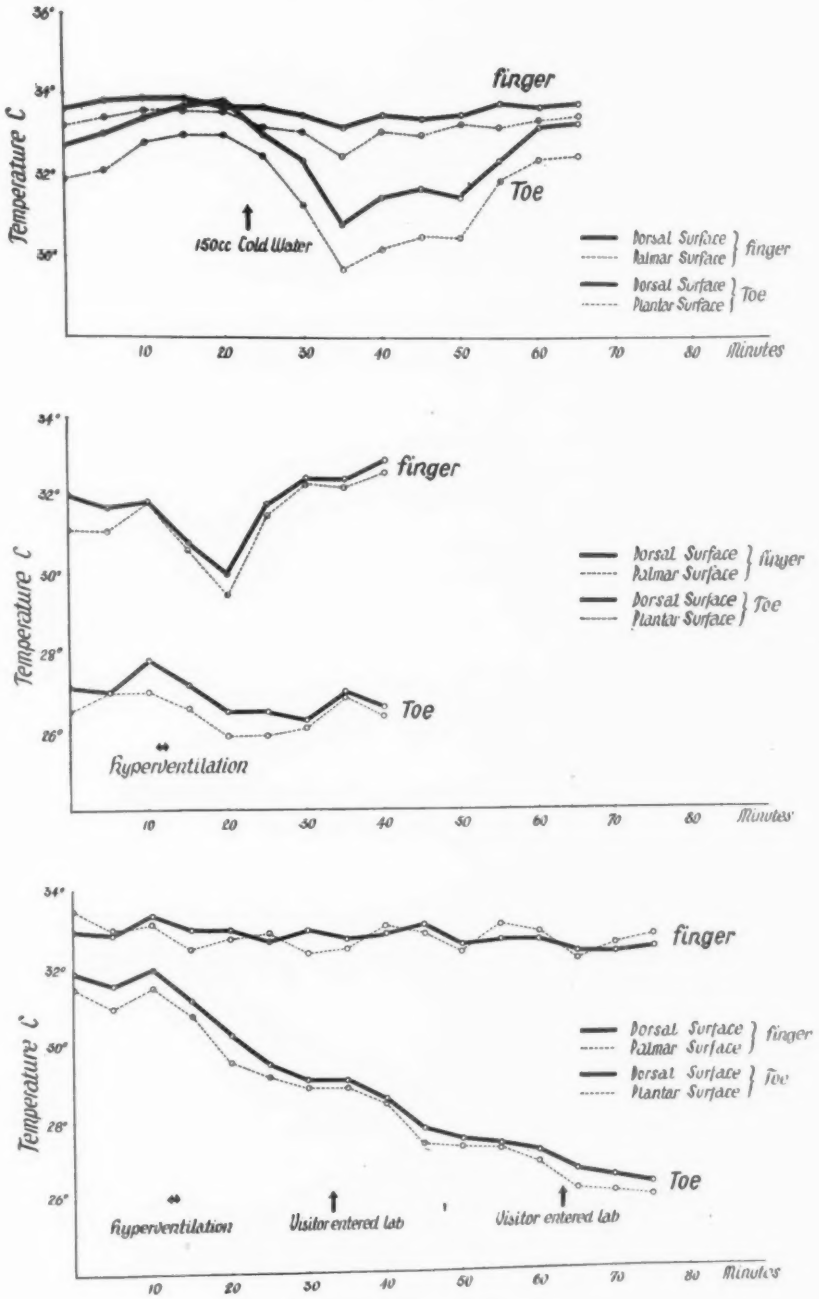
Temperature C
finger
Toe
150cc Cold Water
Dorsal Surface
Palmar Surface
finger
Dorsal Surface
Plantar Surface
Toe
Minutes
Hyperventilation
Visitor entered lab

Fig. 3.

wires long enough to allow limited freedom of movement. The subject of this experiment then busied himself with observations on another subject, the recording of data, and similar activities. On smoking a cigarette a maximum fall in temperature of one-half degree from the control level of 30° C. was recorded. A similar experiment on a second subject yielded essentially the same result. Even though the room temperature was 25° C., the temperature within the shoe was high enough to prevent to a great extent the vasoconstriction caused by smoking, just as in previous experiments in which room temperature was elevated to 30° C.

The skin temperatures of the great toes of two subjects were measured on several successive days immediately after they had returned to the laboratory from lunch. During their absence from the laboratory these subjects spent thirty minutes to an hour walking around outdoors at a temperature of 10° to 12° C., and on one occasion one of the subjects returned with damp shoes and socks because it was raining at the time. Temperature measurements were made as quickly as possible after they entered the laboratory, lest the relatively warm room (25° C.) cause a change. In no instance was the temperature of the great toe found to be less than 30° C., and often it was as high as 33° C. No attempt was made to limit smoking during this period, and on two occasions the subjects were smoking at the time the observations were made. This is not to be interpreted as suggesting that the feet never become chilled when a person spends a considerable period of time outdoors in cold weather. Almost everyone has had experiences to the contrary. However, these observations do indicate that one is frequently able to keep his feet and toes warm and well supplied with blood in spite of smoking and a relatively cool external temperature. Here again one may reasonably assume that the insulation provided by shoes and socks was sufficient to maintain the temperature within the shoes at a level high enough to neutralize the vasoconstrictor effect of smoking, just as was observed in experiments conducted at a room temperature of about 30° C.

From these experiments one may conclude that, during rest and relaxation in the laboratory or hospital, the rate of heat production in the body is so low that there is little or no counteraction against the vasoconstrictor effect of smoking. Once constriction has been produced under these conditions, it may persist for a period of several hours, or until dilatation is caused by the intervention of some other factor, such as an increase in heat production or the more thorough insulation of the body against heat loss. When the rate of heat production is above this low level, as it is when a person is walking or actively engaged otherwise, the necessity for an increase in the rate of dissipation of heat from the body often results in vasodilatation in the feet, even though the atmospheric temperature may be relatively low. Obviously, then, experimental conditions in the laboratory or hospital are not strictly comparable to those under which a person habitually lives.

DISCUSSION

Vasoconstriction in the fingers and toes, regardless of cause, cannot cause a fall in skin temperature to a level much below that of the surrounding atmosphere. If the initial skin temperature is equal to that of the atmosphere, a further decrease from vasoconstriction can hardly be expected. Wright[7] reports that in four of his subjects whose finger temperatures were equal to atmospheric temperature there was no further decrease on smoking. Maddock and Coller[8] report a fall of 5.9° C. in the temperature of the fingers and 1.5° C. in that of the toes after three cigarettes were smoked in rapid succession. That there was a relatively slight change in toe temperature in this experiment was probably because the initial temperature was about 0.4° C. below room temperature, which also fell about a degree during the course of the experiment. The significant change in finger temperature is in keeping with the fact that initially it was nearly six degrees above room temperature.

Many authors neglect to state whether or not inhalation was practiced by their subjects; yet the evidence indicates that this is of great importance in interpreting the results. The smoking of nicotine-free cigarettes, as pointed out above, or the passage of the smoke through water or cotton saturated with ferric chloride solution, as described by Maddock and Coller,[8] suppresses the temperature changes to a marked extent. Also, smoking without inhalation, in nonsmokers, at least, may cause an increase in skin temperature instead of a decrease. Some of the variations in the results which have been reported can probably be ascribed to the fact that some subjects inhaled and others did not.

Apparently, few authors have given more than passing attention to the fact that temperature changes which are often equally as great as those caused by smoking, and not infrequently much more prolonged, are brought about repeatedly during the course of the day by such trivial incidents as drinking a glass of cold water, a sudden noise, reading, or conversation. What, then, is the significance of the fall in skin temperature after smoking? It is difficult to avoid the conclusion that temperature changes, per se, indicate nothing more than sympathomimetic responses, whether they result from smoking or from any one of the various activities of the sort mentioned above which produce comparable changes.

CONCLUSIONS

1. Under most laboratory and hospital conditions the smoking of a cigarette by the average habitual smoker (who inhales) results in the following changes: the systolic blood pressure is increased 10 to 25 mm. Hg; the diastolic blood pressure is increased to approximately the same extent; the pulse rate is increased 5 to 20 beats per minute; and the temperature of the skin of the fingers drops 2° to 5° C., and that of

the toes, 3° to 7° C. Occasionally, greater changes occur in hyperreactive subjects.

2. The smoking of a cigarette by the average nonsmoker (without inhaling) causes only slight changes at most. Generally these are in the same direction as in the habitual smoker, although not infrequently the skin temperature may increase instead of decrease.

3. A comparison of actual temperature curves obtained after smoking with theoretical cooling curves indicates that maximal vasoconstriction rarely persists for more than a few minutes.

4. An environmental temperature of 30° C. inhibits almost completely the peripheral vasoconstriction caused by smoking.

5. Smoking delays warming of the skin of the feet after a cold foot bath. Drinking cold water has a similar effect.

6. Complete removal of the nicotine from cigarettes abolishes almost completely the changes listed in 1. Restoration of the original nicotine content to such cigarettes restores the original effects, indicating that nicotine is the most important agent which contributes to the circulatory and skin temperature changes.

7. Changes in the nature of the respiratory movements during smoking are not responsible for the fall in skin temperature.

8. Various physiologic and psychic stimuli, such as reading, talking, sudden noises, drinking cold water, and hyperventilation, may cause changes in skin temperature comparable to those produced by smoking.

9. Mild physical activity, even at relatively low atmospheric temperatures, inhibits the fall in skin temperature after smoking.

10. Conditions in the laboratory or hospital under which experiments such as the above usually are performed are not strictly comparable to those under which a person lives and indulges in his habitual smoking. Consequently, the results obtained under the one set of conditions are not applicable to the other set of conditions.

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UNUSUAL ARRHYTHMIAS DUE TO MULTIPLE SITES OF CONDUCTION DELAY IN THE A-V JUNCTION IN CASES WITH A SUBSIDIARY VENTRICULAR PACEMAKER LOCATED ABOVE THE BIFURCATION OF THE COMMON BUNDLE

R. LANGENDORF, M.D., AND L. N. KATZ, M.D.
CHICAGO, ILL.

THE electrocardiographic diagnosis of impaired A-V conduction is simple if the ventricles are controlled only by the sinus node. A prolonged P-R interval indicates delayed A-V conduction, and the absence of a ventricular complex following a P wave indicates blockage of the sinus impulse on its way to the ventricles. However, the interpretation of the electrocardiogram becomes more difficult as soon as the ventricles respond to a subsidiary pacemaker as well as to the sinus node, whether the second pacemaker is due to the passive escape of a subsidiary pacemaker below the region of A-V block during ventricular pauses, or to the usurpation of control over the ventricles by an overactive subsidiary pacemaker. In such instances depressed conductivity causing A-V block and interference causing A-V dissociation may coexist and result in complex arrhythmias.[1]

In this report three cases are presented; two are cases of partial A-V block with A-V dissociation of an unusual and rare type,[2-4] and the third represents an example of block in the A-V junctional tissue above (complete) and below (partial) a ventricular pacemaker which is located above the bifurcation of the common bundle of a type hitherto, as far as we know, unreported.

CASE 1.—In this case (Figs. 1 and 2) the P waves are upright in all the limb leads and inverted or diphasic in CF_2; they are alike in each lead, and the P-P intervals are fairly regular. The P-P interval is equivalent to a rate of 65 to 73. In Lead I it is 73; in Lead II, 68 to 70; in Lead III, 65 to 67; and in Lead CF_2, 67 to 70.

The ventricular complexes, on the other hand, show irregular spacing. With the exception of one beat in Lead I, a ventricular premature systole, all the ventricular complexes in each lead are alike. The irregularity of the ventricular complexes shows a definite periodicity. The longer R-R intervals vary in length.

From the Cardiovascular Department, Michael Reese Hospital, Chicago.
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The shorter R-R intervals are practically identical in each lead and are equivalent to a rate of 80 in Lead I, 78 in Lead II, and 77 in Leads III and CF_2. The differences in rate of the ventricles between leads parallel those of the auricles, and both are probably vagal in origin.[5]

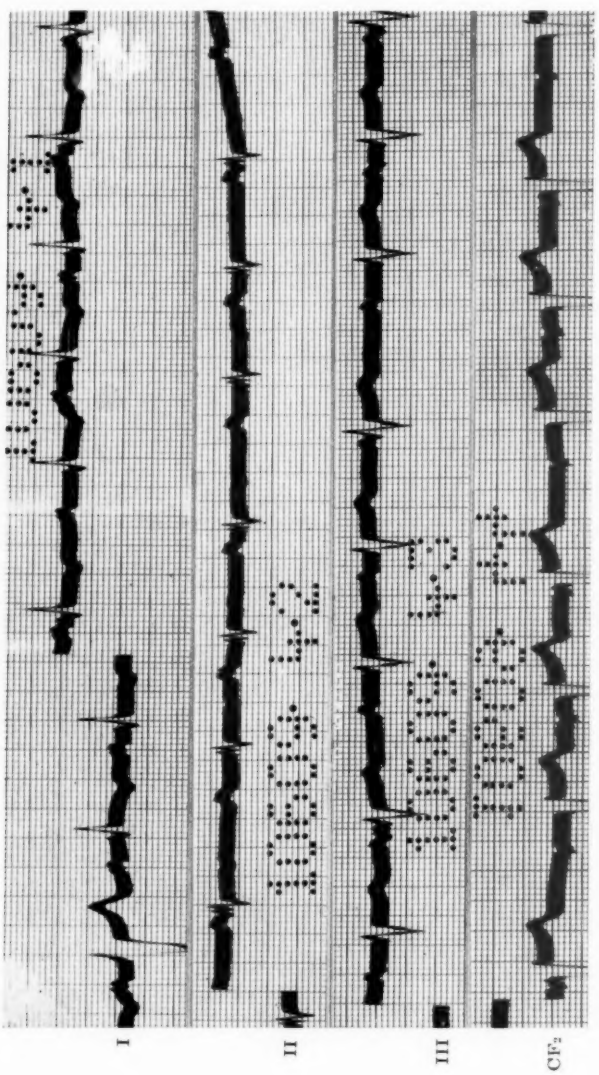

Fig. 1.—Electrocardiogram of Case 1. (The labeling in CF_2 is upside down since the record was taken before the recommendations of the American Heart Association Committee on chest leads was adopted.)

There is no constancy in the relation between P and QRS in this record. The P to QRS time shortens as the short R-R intervals follow each other. When it becomes less than 0.16 sec. (actually 0.10 to 0.16 sec.), a long R-R interval invariably follows.

The presence of regular ventricular activity at a rate higher than the auricular and the progressive shortening of P-R distances at such times indicate that there is a ventricular pacemaker distinct from the sinus node in control of the ventricles, at least at times. In these beats there is apparently interference between

the impulses coming down from the auricle and those traveling toward the auricles from the ventricular pacemaker. The ventricular rhythm arises above the bifurcation of the common bundle and presumably in the A-V node, in spite of a QRS duration of 0.12 sec., since the ventricular complexes in this record are practically identical with those in records taken three days previously and fifteen days later with normal sinus rhythm and prolonged P-R time (Fig. 3).

The occurrence of the longer R-R intervals is ascribed to the absence of discharge of the ventricular pacemaker at the expected time. During these intervals, apparently unlike other cycles, the sinus impulse reaches and discharges this subsidiary pacemaker[2-4] but is itself blocked lower in the A-V junction and fails to stimulate the ventricles. The presence of first degree A-V block in records before and after (Fig. 3) this one would favor the presence of such blockage.

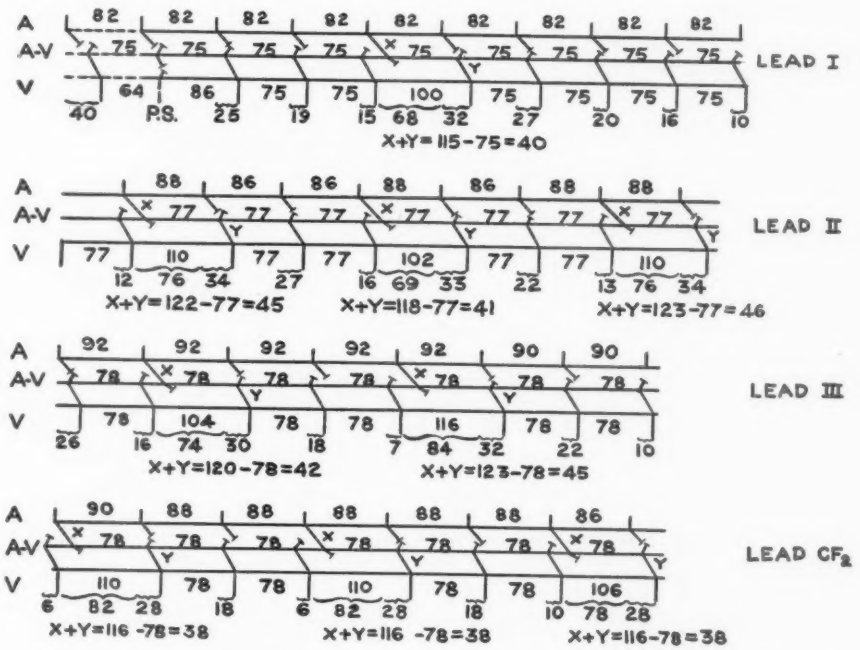

Fig. 2.—Analysis of record shown in Fig. 1. *A* is the auricular stimulation as marked by the beginning of the P waves; *V* is the ventricular stimulation as marked by the beginning of QRS; and *A-V* is the time of discharge of the A-V nodal pacemaker set an arbitrary distance ahead of *V*. *X*, *Y* and *X* + *Y* are described in the text. The figures in the lowest line of each lead represent P-R distances (and in the longer pauses R-P distances as well). *P.S.* is a premature ventricular systole. The values on lines *A*, *A-V*, and *V* give, respectively, the intervals between P waves (P-P interval), the discharge of the ventricular pacemaker, and the intervals between QRS complexes (R-R interval). The time values are in $\frac{1}{100}$ of a second, viz. 99 is 0.99 seconds, etc. Discussed in text.

The nature of the ventricular response which terminates the long pause is not immediately ascertainable. The choice lies between a conducted sinus impulse so that the P-R represents transmission time, or an impulse arising from the ventricular pacemaker reaching the ventrices before the next sinus impulse. We incline to the latter view primarily because the P-R distance of the beats at the end of the long pauses seem to vary directly with the preceding R-P distance rather than as the inverse of the latter which would be the case if the ventricular complexes were due to impulses of sinus origin. Apparently the discharged ventricular pacemaker can rebuild and discharge again before another sinus impulse can reach it.

The R-R distance of the longer pauses varies inversely with the P-R distance of the beat before the pause. This would imply that, as the P-R distance shortens, sinus impulses reach and discharge the ventricular pacemaker later in its cycle. This is also supportive evidence that the ventricular beat after the pause is not sinus in origin.

An idea of the transmission time from the sinus node to the ventricular pacemaker (X) plus that from the latter to the ventricles (Y) can be obtained by subtracting the R-R interval of the shorter ventricular cycles from the time interval between P ahead of the pause to QRS after the pause. We have found no method for determining the relative times of the two components. The values obtained for their sum (X + Y) equal 0.38 to 0.46 sec. and compare reasonably with the P-R intervals found before and after this record was taken (0.50 sec. and 0.36 sec., respectively). However, it has been shown[6, 7] that premature discharge of a ventricular pacemaker may cause a depression of the pacemaker, so that the value assumed for the cycle length of the ventricular pacemaker after its discharge by the sinus impulse may be too short, and hence the value for the conduction times, X + Y, may be too long.

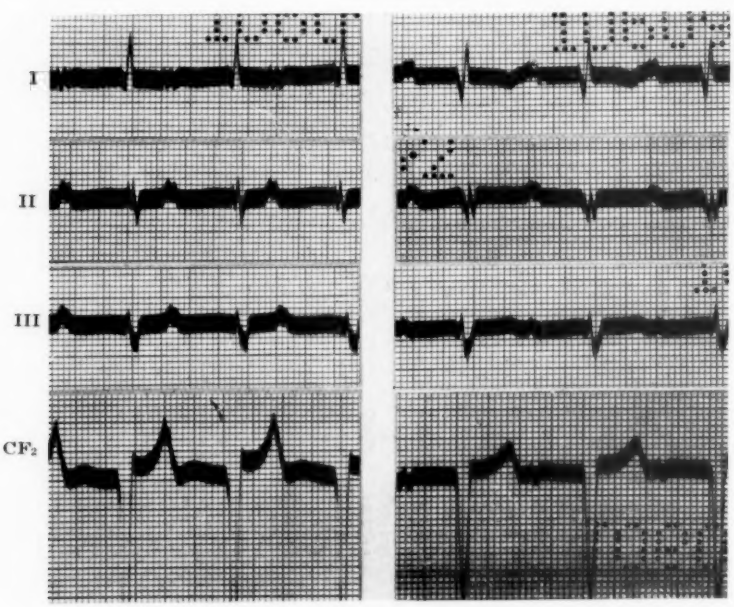

Fig. 3.—Records *A* and *B* of Case 1 taken respectively three days before and fifteen days after the record shown in Fig. 1. Discussed in text.

The ventricular premature systole (*P.S.*) at the beginning of Lead I apparently did not disturb the timing of the ventricular pacemaker, indicating that this premature ectopic impulse did not reach and discharge the regular ventricular pacemaker or that it reached it just when it was due to discharge.

In brief, this is a case of A-V dissociation due to the activity of a subsidiary pacemaker located above the bifurcation of the common bundle, presumably within the A-V node. The rate of this ventricular pacemaker exceeds that of the sinus node. It is associated with a constant retrograde block located somewhere in the A-V junctional tissue above the ventricular pacemaker. In addition, there is evidence of (forward) A-V block, since P waves falling in diastole outside the normal refractory period of the A-V junctional tissue and with sufficient time for

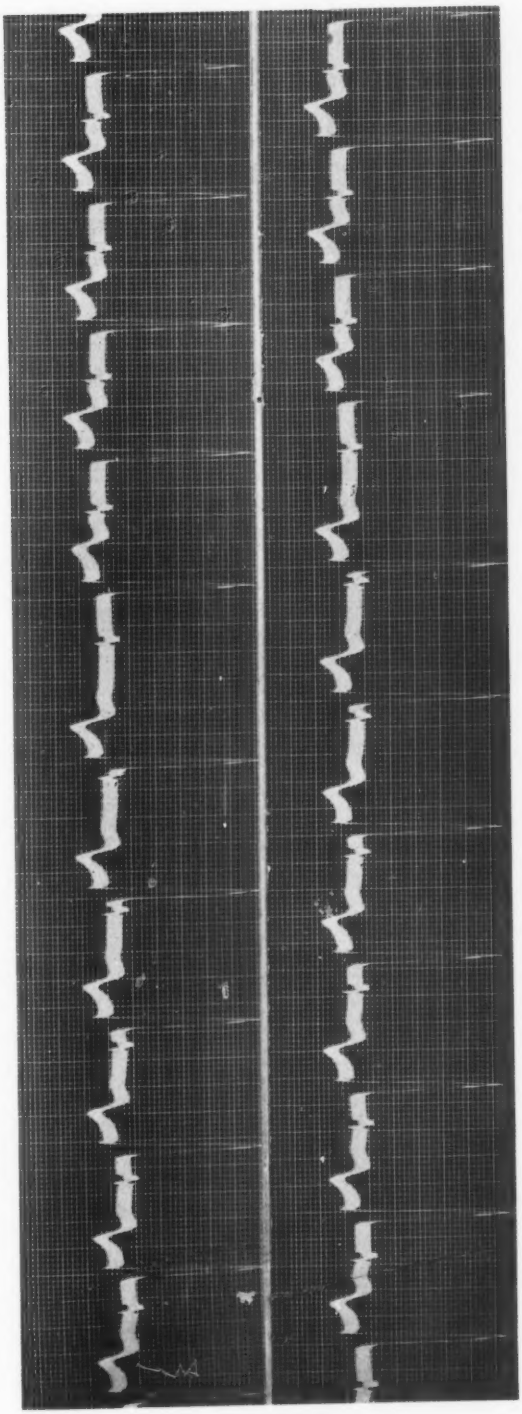

Fig. 4.—A continuous strip of Lead CF_2 of the record of Case 2 analyzed in Fig. 5 and discussed in text.

a P-R of normal duration to occur do not give rise to a ventricular response. Some ventricular beats occur under exceptional conditions and may at first appear to be conducted beats, but on further analysis this seems unlikely.

The unusual phenomenon that distinguishes this case of A-V dissociation from the usual type is the peculiar arrhythmia of the ventricular pacemaker. This is caused by the sinus impulse which sometimes arrives after the absolute refractory phase of the region in the A-V junction above the ventricular pacemaker and discharges the ventricular pacemaker without being conducted through to the ventricles.

Although there is not one ventricular beat resulting from an impulse in the sinus node, there is evidence that conduction is possible along the whole pathway from the sinus node to the ventricular muscle, since conduction occurs in some beats from the sinus node to the site of the ventricular pacemaker and in many other beats from this point to the ventricles. In this case, therefore, there is a permanent retrograde A-V block, complete A-V dissociation, and partial (forward) A-V block. The retrograde block is nearest the auricles, and the complete dissociation occurs below it; both are located above the ventricular pacemaker. The partial (forward) A-V block, however, is located in part between the ventricular pacemaker and the ventricles.

CASE 2.—This case (Figs. 4 and 5) shows essentially the same arrhythmia as Case 1, namely, complete A-V dissociation. The auricles are controlled by the sinus node, and the ventricles, by a ventricular pacemaker located above the bifurcation of the common bundle, presumably in the A-V node. Long ventricular pauses also occur (whenever the P-R distance becomes less than 0.11 sec.). The ventricular pauses are less frequent in this case than in the previous one because there is less difference between the rate of the sinus node and the ventricular pacemaker. Long pauses actually occurred only three times in a record containing 50, 50, 50, and 67 successive cycles in the three limb leads and the one chest lead (the last two are shown in Figs. 4 and 5).

The rate of the sinus node varies from 58 to 68; that of the ventricular pacemaker, from 61 to 68. When the rates of the two pacemakers are almost identical, the relation of P to QRS remains constant for many cycles and superficially suggests a sinus rhythm with 1:1 conduction and a prolonged P-R interval. However, examination of the entire Lead CF_2 record proved conclusively that A-V dissociation is actually present throughout, although becoming more evident whenever the rate of one pacemaker changes without corresponding change in the rate of the other.

The long ventricular pauses in this case occur only when the preceding P to QRS distance is 0.11 sec. or less (0.10; 0.08; 0.11 sec.). The interval from P preceding the long ventricular pause to QRS after the pause is fairly constant measured 1.42, 1.36, and 1.39 sec. The nature of the beat following the long ventricular pause is more difficult to determine than in Case 1. However, for similar reasons,

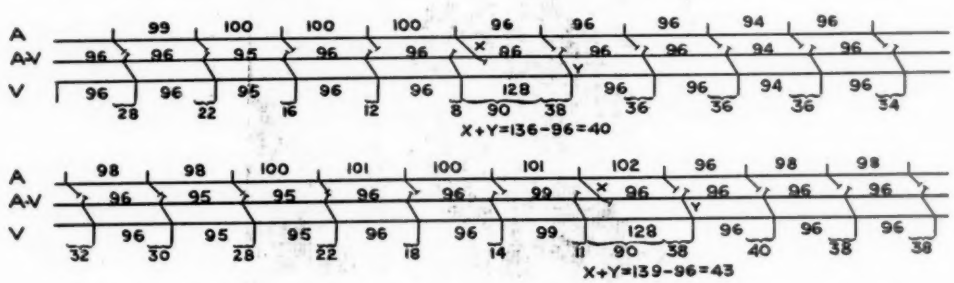

Fig. 5.—Analysis of record shown in Fig. 4. Conventions as in Fig. 2. Discussed in text.

the beats terminating the long ventricular pauses are probably not due to conducted sinus impulses. The distance from QRS ahead of the pause to the P during the pause was constant in all three pauses (0.90 sec.), and therefore the distance from P during the pause to QRS terminating the ventricular pause would be expected to be constant if this latter were a conducted beat. Actually, the P-R distance after the pause measures 0.41, 0.38, and 0.38 sec. These differences can be explained on the assumption that the beats after the pause are ventricular beats since the longer P-R distance of 0.41 sec. is associated with slowing of the ventricular pacemaker.

The sum of the conduction time from the auricles to the site of the ventricular pacemaker (X) and that from this point to the ventricles (Y) equals 0.42, 0.40, and 0.43 sec., indicating the presence of partial (forward) A-V block.

This, then, is another instance of A-V dissociation with permanent retrograde A-V block, both located above the ventricular pacemaker, and partial (forward) A-V block located somewhere below the ventricular pacemaker. The latter occurs on these occasions when the sinus impulse discharges the ventricular pacemaker and fails to reach the ventricles.

CASE 3.—This record was taken on a "digitalized" patient, and the effect of the drug is reflected in the contour of the S-T-T complex (Fig. 6). No P waves are seen in any of the three leads; instead, there are fine oscillations of the base line indicating fibrillation of the auricles.

The ventricular complexes are of the supraventricular type and show irregular spacing. However, as shown in Table I, all but two of the R-R intervals fall into one of two groups; they are either short (0.84 to 0.88 sec.) corresponding to a rate of 68 to 71, or long (1.66 to 1.74 sec.) corresponding to a rate of 35 to 36. Because the long R-R intervals are almost exactly twice as long as the short ones and are fairly constant, it is unlikely that they are due to impulses conducted from the fibrillating auricles to the ventricles. It is more likely that these ventricular beats are responses to a regularly discharging pacemaker located above the bifurcation of the common bundle, presumably the A-V node, which are conducted through a depressed region in the A-V junction which leads, at times, to a dropping out of every other impulse, viz., partial block (intermittent 2:1) between the ventricular pacemaker and the ventricles. This further presupposes the presence of complete A-V block between the auricles and the ventricular pacemaker.

TABLE I

DURATION OF SUCCESSIVE R-R INTERVALS IN 0.01 SEC.

Lead I	88, 85, 85, 84, 85, 84
Lead II	166, 166, 124, 84
Lead III	174, 172, 170, 108

However, there are two R-R intervals, the third in Lead II and the fourth in Lead III, measuring 1.24 and 1.08 sec., respectively, which do not fit into either of the above categories. The length of these intervals can be explained if it is assumed that the block below the ventricular pacemaker is of the type associated with the Wenckebach phenomenon (Fig. 7).

Although we cannot determine the conduction time from the ventricular pacemaker to the ventricles, its duration should be longer when 1:1 conduction is present than when every other beat is blocked. Since the third R-R in Lead II occurs on resumption of 1:1 conduction, the transmission time of the beat before this interval should be considerably shorter than the conduction time of the beat following. Once 1:1 conduction is established, the prolonged conduction time would remain approximately constant and the R-R interval would then correspond

to the cycle length of the ventricular pacemaker. Thus the difference in conduction time from the ventricular pacemaker to the ventricles of the last beat of 2:1 block and that of the next beat is responsible for the lengthening of the transitional R-R interval. The difference between this R-R and that of established 1:1 conduction measures 0.41 sec. in Lead II and presumably would have been 0.21 sec. in Lead III if one assumes that the R-R interval of 1:1 conduction after the transitional R-R interval would have measured half the longest R-R interval. It is regrettable that longer strips of this record were not available.

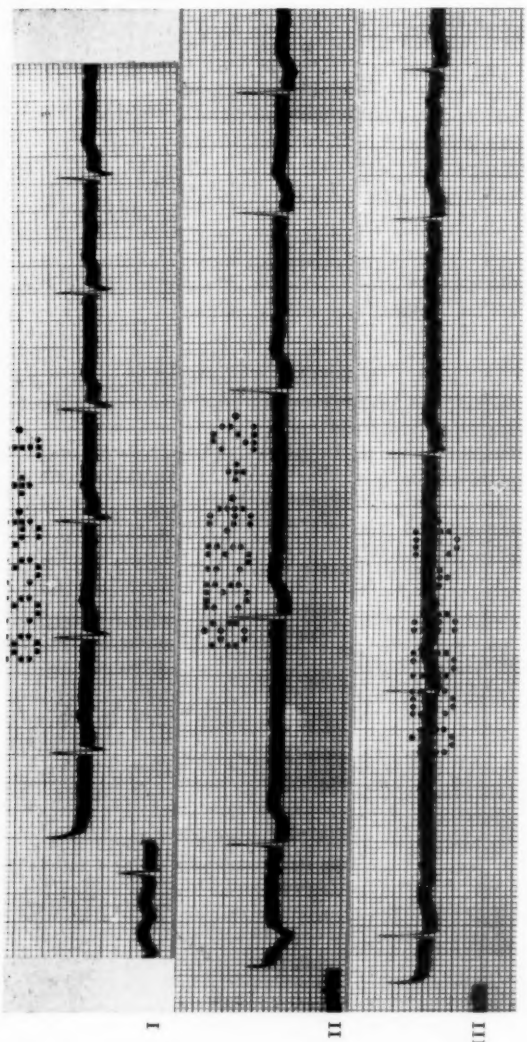

Fig. 6.—Electrocardiogram of Case 3; Lead II of this record is analyzed in Fig. 7. Discussed in text. The record shows "overshooting," but this does not obscure the digitalis effect on the S-T-T.

In brief, this is a case of auricular fibrillation in which digitalis produced a *complete* A-V block and the ventricles were controlled by a subsidiary pacemaker above the bifurcation of the common bundle, presumably the A-V node. However, the A-V junctional tissue below this pacemaker was also in a depressed state and thus unable to transmit without delay the impulses initiated by the ventricular pacemaker. At times, there was a simple delay in conduction; at other times,

there was a dropping out of every other impulse associated with a shortening of the conduction time of the conducted beats. Because of the changes in conduction time at the transition from 2:1 to 1:1 rhythm an R-R interval appeared that was longer than those after 1:1 conduction was established and exactly like that found in the Wenckebach phenomenon.

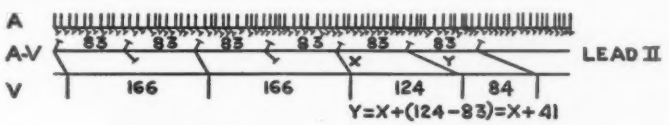

Fig. 7.—Analysis of Lead II of record shown in Fig. 6. *A* represents the auricular stimulation; however, no attempt is made to reproduce the exact time of the stimuli; only their rapidity and irregularity are shown and their blockage above the A-V pacemaker is indicated. *X* is the usual time arbitrarily assumed as the conduction time from the A-V pacemaker to the ventricles. *Y* is the lengthened conduction time in the second beat after the ventricular pause (the Wenckebach phenomenon). The other conventions are as in Fig. 2. Discussed in text.

COMMENT

The three cases present one common feature; they all show evidence of two regions in the A-V junction and common bundle in which impulses are prevented from passing either all the time or on occasion. In the first two cases there is interference and retrograde block above the ventricular pacemaker and blockage of the supraventricular impulse below the ventricular pacemaker on occasion. In the third case there is complete block above the ventricular pacemaker and partial block below it. The normal duration of QRS of the ventricular beats in Cases 2 and 3 and the identity with beats of sinus origin in a preceding record in Case 1 indicate that the ventricular pacemaker in all three is located above the bifurcation of the common bundle, presumably in the A-V node. The absence of auricular responses to the ventricular pacemaker makes it impossible to determine its site more accurately. The depressed region where the delay or complete blockage of the impulse to the ventricle occurs lies below the ventricular pacemaker and above the bifurcation of the common bundle; its accurate localization depends on that of the ventricular pacemaker and thus remains undetermined. It would appear that, if the ventricular pacemaker is located in the upper part of the A-V node, the delay, or block, could occur in the lower part of the node; thus the delay does not necessarily have to be located in the common bundle, as was assumed by Scherf,[8] when he explained the apparent shortening of the first idioventricular cycle in cases of A-V dissociation.

SUMMARY

Three cases of unusual arrhythmias associated with a ventricular pacemaker located above the bifurcation of the common bundle, presumably in the A-V node, are reported.

In Cases 1 and 2 complete A-V dissociation is present. Certain sinus impulses, however, reach and discharge the ventricular pacemaker, but they are blocked below this point and thus are prevented from stimu-

lating the ventricles. However, it is evident from the analysis presented that conduction is possible along the whole A-V conduction pathway. The sum of the conduction time from the auricles to the ventricular pacemaker and from this point to the ventricles can be determined and, when measured, indicates delayed A-V conduction.

Case 3 shows auricular fibrillation with complete A-V block above the ventricular pacemaker and partial A-V block with the Wenckebach phenomenon in a region between the ventricular pacemaker and the bifurcation of the common bundle.

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ATHEROMATOSIS OF THE MITRAL VALVE

C. Alexander Hellwig, M.D.
Wichita, Kansas

A PREVIOUS study[1] of coronary sclerosis in sixty-two autopsy cases led to the following conception of the genesis of atherosclerosis. The earliest lesion is an accumulation of finest lipoid granules in the ground substance of the intima. The source of these lipoid deposits is the blood plasma which nourishes the intima. The retention of lipoid in the intima is favored by a high-cholesterin content of the blood plasma and by a disturbance of the lymph flow in the intima.

The next step in the development of atherosclerosis is the appearance of fat-filled cells which have taken up the lipoid from the ground substance. During the ascending period of life accumulation of fat in the intercellular substance and in the cells of the intima is not associated with proliferation of connective tissue, and destructive changes characteristic of advanced atherosclerosis are entirely absent.

In middle life, an extensive fibroplastic process arises in the diseased arteries. Following injury of the tissue by the accumulation of lipoid, granulation tissue develops. At first many small blood vessels are present in the young connective tissue. They originate from vasa vasorum of the media, and they may communicate directly with the lumen of the diseased artery. After collagenous fibers have been formed, the vascular tissue loses its blood vessels, and a dense hyaline scar results. This cuts off the lipoid deposits from blood and lymph supply, and the fat-laden cells and fibers become necrotic. The space occupied by dead cells is converted into a cavity filled with detritus, cholesterol crystals, and fluid; this is the so-called atheromatous abscess.

If this abscess ruptures into the lumen of the artery, ulceration of the wall and thrombosis may occur. From the lumen of the diseased vessel, blood may invade the intima, causing hematomas in the wall. Calcification of the necrotic area in the intima occurs after the liberation of glycerin and crystalline cholesterin and the formation of insoluble calcium soaps. This completes the picture of atherosclerosis.

The results of my previous study showed that the whole process of atherosclerosis is initiated and governed by deposits of cholesterin in the intima, and that the destructive changes in the diseased vessel depend upon the fibroplastic reaction of the intima. This conception of

From the Department of Pathology, St. Francis Hospital.
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TABLE I

SUMMARY OF MORPHOLOGIC FINDINGS IN 100 CASES OF ATHEROMATOSIS IN ANTERIOR LEAFLET OF MITRAL VALVE

CASE	SEX	AGE (YR.)	CLINICAL DIAGNOSIS	GROSS LOCALIZATION			MICROSCOPIC FINDINGS	
				MEDIAL	CENTRAL	LATERAL	FIBRO-ELASTIC	MIDDLE PLATE
1	M	2	Bronchopneumonia	+			++	
2	F	2	Bronchopneumonia		+		+	
3	F	3	Little's disease	+			+	
4	M	9	Poliomyelitis		+		++	
5	M	11	Liver rupture		+		++	
6	F	11	Peritonitis	+	+	+	++	
7	M	14	Rheumatic heart	+			++	
8	M	16	Cavernous sinus thrombosis		+		++	
9	M	16	Brain tumor		+			
10	M	19	Lung gunshot	++			+	
11	M	21	Peritonitis	++			++	
12	M	27	Acute myocarditis	++			++	
13	M	24	Encephalitis		+			
14	F	25	Lobar pneumonia	+	+	+		
15	M	30	Ulcerative endocarditis		+			
16	M	35	Appendicitis	+	++	+		
17	M	36	Septic endocarditis	+	+		++	+
18	F	38	Syphilis		++			
19	F	38	Peritonitis		++			
20	M	39	Ulcerative endocarditis	+	++	+		
21	M	38	Coronary occlusion	++	++			
22	M	40	Lung abscess			+	+	+
23	M	40	Influenza pneumonia	+	++	++	++	++
24	M	41	Syphilitic aneurysm			+++	+++	++
25	M	42	Coronary occlusion	+++	++	+		
26	M	44	Strychnine poisoning	+	+++			
27	F	45	Diabetes		+++			
28	F	45	Mitral stenosis	+				
29	M	46	Glomerulonephritis	+	+++			
30	M	46	Coronary occlusion	+++	++			
31	M	47	Coronary occlusion	+	+++	+		
32	M	47	Anesthesia death	+	+++	+		
33	F	47	Carcinoma coli	+	+++	+	+++	++
34	F	48	Carcinoma of cervix	+	++	+	+++	+++
35	M	49	Coronary occlusion	+	+++	++		
36	M	49	Pneumonia, hypertension	++	+++	++	+++	++
37	M	49	Hypertension		+++		++	+++
38	M	50	Arsenic poisoning	++		++	++++	++
39	M	50	Skull fracture	+	++	+		
40	F	50	Rupture of aorta	+	++	+		
41	F	50	Carcinoma of ovary		++		+++	++
42	M	50	Coronary occlusion	+	+++	+	++	++
43	M	52	Heart gunshot	++	++		++	++
44	M	52	Apoplexy		++	+		
45	M	53	Anesthesia death	+	+	+		
46	M	54	Ulcerative endocarditis		++			
47	F	54	Peritonitis	++	++	+	++	+++
48	M	54	Coronary occlusion	++	++	++	++	++
49	F	55	Aortic stenosis	++	++		++	++
50	M	55	Nephrosclerosis	+	++	+	++	+++
51	M	55	Coronary occlusion		+++			
52	M	55	Rupture of aorta		++			
53	F	56	Bronchial asthma	++	+	+	+++	+++
54	F	57	Liver rupture		++	+		

TABLE I—CONT'D

CASE	SEX	AGE (YR.)	CLINICAL DIAGNOSIS	GROSS LOCALIZATION			MICROSCOPIC FINDINGS	
				MEDIAL	CENTRAL	LATERAL	FIBRO-ELASTIC	MIDDLE PLATE
55	M	57	Leucemia		+++			
56	F	57	Pneumonia	++				
57	F	57	Pulmonary embolism		++			
58	M	58	Coronary occlusion	+	++	+		
59	M	60	Dissecting aneurysm		+++			
60	F	60	Perforating stomach ulcer	++	++	++		
61	F	60	Streptococcic pyemia	+++		++	++	++
62	F	60	Pulmonary embolism	+	+++	+	++	+++
63	M	62	Hypertension	+	+	+	++	+
64	M	62	Coronary occlusion	+	+++	+		
65	M	63	Coronary occlusion	+	+++	+		
66	M	63	Diabetes, coronary occlusion	+	++	++	++	++
67	M	63	Coronary occlusion	++	+++	++		
68	M	64	Carcinoma of tongue		++		+++	++
69	F	65	Coronary occlusion	+++	+	+++		
70	F	65	Rupture of heart	++	+++	++		
71	M	67	Syphilis of aorta	+		+	++	+++
72	M	67	Hypertension	++	+++	++		
73	M	67	Diabetes	+	++	+	+++	+++
74	M	68	Apoplexy	+	+++	++	+++	++
75	M	68	Liver cirrhosis	+	+++	+	++	+++
76	F	68	Myocardial infarct	+	++	+		
77	F	68	Oral carcinoma	++	+++	++	+++	+++
78	M	69	Ulcerative endocarditis	+	+++	++	++	+++
79	F	70	Coronary occlusion	++	++	++	++	+++
80	F	71	Coronary occlusion	+	++	+	+++	++
81	F	71	Intestinal obstruction	+	++	+		
82	M	71	Aortic stenosis	+++	++	+		
83	M	72	Uremia	+	+++	+	++	++++
84	M	74	Bronchopneumonia	++	+++	++	+++	+++
85	M	74	Stomach carcinoma	+	+	+	+++	+
86	F	77	Bronchopneumonia	+	++	+		
87	M	78	Coronary occlusion	+	+	+		
88	M	78	Cholecystitis	++	+++	++	++	+++
89	M	80	Pyonephrosis, diabetes	+	++	+		
90	M	81	Hypertension	+	++			
91	M	81	Bronchopneumonia	++	++	++		
92	F	81	Apoplexy	+	+++	+		
93	M	81	Hypertension	++	++	++	++	+++
94	M	81	Perforation of rectum	++	++	++	+++	+++
95	F	81	Lobar pneumonia	++	++	++	+++	+++
96	M	82	Bronchopneumonia	++	++	++		
97	M	84	Myocardial infarct	++				
98	M	84	Bronchopneumonia	+	+++	+	++	+++
99	M	86	Apoplexy	+++		+	+++	+++
100	M	87	Coronary occlusion	+	+++	+	++	++

the genesis of atherosclerosis conforms with the view held by Aschoff,[2] Anitschkow,[3] and Leary[4] that imbibition of the intima with cholesterin plays the foremost role in atherosclerosis.

In a colorful monograph,[5] Winternitz, Thomas, and LeCompte reported their studies on the biology of arteriosclerosis. By clearing arteries with glycerin, these investigators noticed hemorrhages in the intima at the site of predilection of arteriosclerosis. They contended

that the primary cause of atherosclerosis is rupture of vasa vasorum which, in their opinion, are normally present in the intima. Hemorrhagic diathesis, vitamin deficiencies, mechanical, chemical, and bacterial agents are, according to them, responsible for increasing the permeability of the capillary wall and for causing hemorrhages in the intima. If absorption or organization of these intimal hemorrhages is not complete, the residuum remains as a necrotic focus, the so-called atheromatous abscess.

The conclusions by Winternitz and his co-workers were so much at variance with my own observations that I studied the atheromatous process in structures which are generally regarded as devoid of blood vessels, namely, heart valves.

The present paper is based on the examination of the mitral valve in 100 autopsy cases. After the gross findings were noted, frozen and paraffin sections were made from the cusps and the following staining methods were employed: Sudan III and hematoxylin, hematoxylin and eosin, orcein and van Gieson stain.

My youngest subject was 2 years old; the oldest, 87 years. The gross and microscopic findings are listed in Table I.

GROSS APPEARANCE

Without exception, yelllow spots were found only on the ventricular side of the anterior leaflet of the mitral valve and never on the auricular surface. The significance of this predilection will be discussed later.

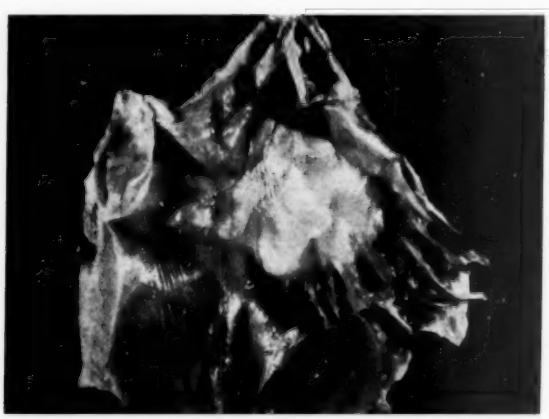

Fig. 1.—Anterior mitral leaflet of a 55-year-old male. Ventricular side with maplike deposits of lipoid.

In early childhood the yellow areas are most often located near the medial and lateral margin of the leaflet. The next most frequent site of lipoidosis is at the insertion of the chordae tendineae. In older people, the chordae themselves are always involved in the process, but again only on the ventricular side. The yellow spots are either completely flat and

within the surface of the valve or slightly raised. Some are sharply defined; others, very indistinct. Their form is round, oval, or irregular maplike. The size varies from 1 mm. to more than 1 cm. At the insertion of the chordae the yellow spots are often triangular, radiating from the cord into the leaflet. In later years, bandlike deposits are found running across the whole leaflet, especially in the upper third. There are often several parallel yellow streaks, between 1 and 3 mm. wide.

Fig. 2.—Anterior mitral leaflet of an 82-year-old male. Bandlike deposits of lipoid on ventricular side.

Fig. 3.—Anterior mitral leaflet of a 71-year-old female. Magnification, ×2. The discontinuity of the lipoid deposits is well shown.

MICROSCOPIC FINDINGS

The normal microscopic structure of the anterior leaflet of the mitral valve has been studied by Sato[9] and Saltykow,[10] and my own findings are in complete agreement with their description. The leaflet has a fibrous middle plate which is covered on both sides with identical layers. Starting from the ventricular surface the following layers can be dis-

tinguished: (1) the endothelium with the subendothelial connective tissue, (2) the elastic layer, (3) the fibroelastic layer, then the middle plate, and, in reverse order, the fibroelastic layer, the elastic layer, the subendothelial connective tissue, and, finally, the auricular endothelium.

The earliest microscopic alterations are deposits of fine lipoid granules in the subendothelial and the fibroelastic layers on the ventricular side of the leaflet. While in many cases fat-laden cells are present at the same time, it can be demonstrated that fatty materials are deposited in the ground substance of the valve before any fat-containing cells are found. The extracellular lipoid may be masked by the advent of numerous cells which become laden with fat. At a slightly later stage, the fibroelastic layer contains a considerable accumulation of cells among which large foamy cells resembling xanthoma cells are the most conspicuous. Their outline is rounded or polygonal, sometimes flattened. The nucleus is usually centrally placed, small, round, and deeply staining. In the interstices between the fibers of the fibroelastic layer, there are found other, much smaller, spindle-shaped or stellate cells with round or oval nuclei. Many of the spindle cells contain fatty granules scattered in the protoplasma at either end of the nucleus. These cells are morphologically indistinguishable from fibroblasts.

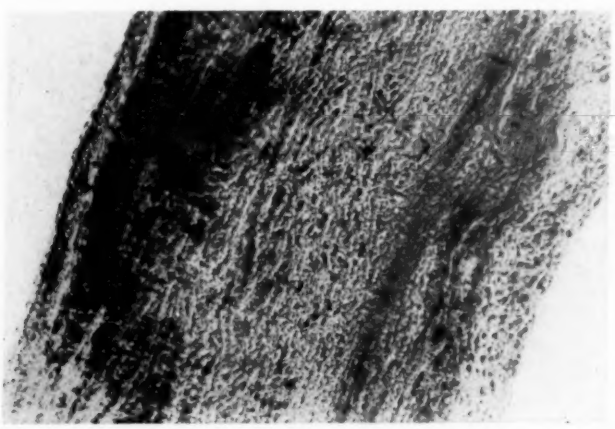

Fig. 4.—Anterior mitral leaflet of a 50-year-old male. Magnification, ×50. The deposits of lipoid (dark stained) are found in the ventricular layers only.

After the thirtieth year the amount of lipoid deposits increases, and the fatty material extends farther and farther downward from the ventricular side, until, after the age of 40, most of the middle plate is impregnated with lipoid. With advancing age, many collagenous fibers of the middle plate appear poorly defined and, when stained with hematoxylin and eosin, small areas of necrosis become evident. Crystals of cholesterin together with finest granules of calcium accumulate in the necrotic areas. In not a single instance, however, was this process so

extensive that atheromatous abscesses or calcified plaques were seen with the unaided eye. Contrary to atherosclerosis as found in blood vessels, proliferation of vascular connective tissue was never noticed in the diseased heart valve. Blood vessels were entirely lacking around the deposits of cholesterin crystals and calcium, and no scar tissue was formed. The complete absence of reactive processes and of destructive lesions in atheromatosis of the heart valves is in striking contrast to lesions as observed in arteries.

COMMENT

There are five papers[6-10] in the literature dealing with atheromatosis of the mitral valve. While all observers agree in the exclusive involvement of the ventricular side of the large mitral leaflet, the significance of this fact has apparently been overlooked. Its importance in regard to the genesis of atherosclerosis cannot be overestimated. This observation disproves at least six theories which play an important role in recent discussions of the atherosclerosis problem.

1. The predilection of the process to the ventricular side of the leaflet does not support the theory that arteriosclerosis is a manifestation of a specific disease of fibroelastic tissue throughout the body, caused by wear and tear (Kolen[11]). Both sides of the mitral leaflet have identical arrangement of collagenous and elastic fibers and are subject to the same degree of wear and tear.

2. The localization of the lipoid deposits is in contradistinction to Hueck's[12] theory that changes in the hydrogen-ion concentration of the ageing intima lead to the process of atherosclerosis. There can be no difference in pH between the ventricular and auricular layers, since both have the same histologic structure and are suspended in the same nourishing medium, namely, arterial blood.

3. The site of the yellow spots disproves the assumption of Winternitz, Thomas, and LeCompte, who believed that rupture of vasa vasorum initiates the process of atherosclerosis. There are no blood vessels in the free portion of the normal mitral leaflet; occasionally in the upper third, blood vessels may be encountered accompanying muscle bundles, and, in cases of rheumatism, they may be found in the other parts of the cusp. However, such vessels as are in the leaflet are seen only on the auricular side, i.e., just opposite the localization of yellow spots.

4. The complete absence of proliferation of fibrous tissue, which is characteristic of atheromatosis of the mitral valve, does not substantiate the assumption of Jores,[13] who believed that fibrous thickening of the intima invites the precipitation of lipoid. In mitral valves, a new formation of connective tissue does not exist, but deposits of cholesterin, formation of cholesterin crystals, and calcification occur as in blood vessels.

5. My findings do not support the view held by Duff[14] that a primary degeneration of the ground substance of the intima is the essential cause of arteriosclerosis and that it precedes the precipitation of lipoids. An alteration of the ground substance on the ventricular side only, with subsequent lipoidosis, seems very unlikely.

6. The predilection of the yellow spots to the ventricular layers is not in accord with the view held by Jones and Rogers[15] that the endothelium may become permeable for cholesterin after injuries by bacterial influences. Bacterial lesions are, as a rule, found on the auricular side of the mitral valve.

The results of my own studies are in accord with the conception of Anitschkow that precipitation of lipoid in the ground substance is the essential cause of atherosclerosis and that it occurs without previous degeneration of the ground substance.

The whole problem of atherosclerosis then hinges upon the question of why lipoids precipitate from the nutrient fluid in the ground substance. Since the lipoids enter the tissue of the leaflet on the ventricular and auricular side with the nourishing blood plasma, the question is "Why do they precipitate only on the ventricular side?"

The lipoids appear in the nourishing fluid in colloid solution. There have to be certain factors which disturb the stability of this colloid solution on the ventricular side. With every ventricular systole, the colloid solution in the tissue of the mitral leaflet is subjected to vigorous percussions. The fluid waves which start from the ventricular surface of the leaflet are broken at the fibrous middle plate, and the fluid in the ventricular fibroelastic layer suffers repercussions in opposite direction. From the fundamentals of colloid chemistry it seems plausible that these mechanical forces are responsible for the precipitation of lipoids in the ground substance of the ventricular layers. The importance of mechanical influences on the precipitation of colloid particles is known from flocculation tests. Kahn,[16] who studied in detail the shaking principle in flocculation tests, demonstrated that excessive shaking leads to flocculation of lipoids even in normal sera.

SUMMARY

The morphologic findings in 100 mitral valves with atheromatosis are presented. Anitschkow's view, that precipitation of lipoids in the ground substance is the primary event of atherosclerosis and is not preceded by degeneration of the tissue, is accepted.

Lipoids enter the leaflet with the nourishing blood plasma, in colloid solution. The localization of the atheromatous lesions on the ventricular side of the leaflet refutes many theories on the cause of arteriosclerosis and suggests the importance of mechanical factors. The nourishing fluid in the ventricular layers of the mitral leaflet is subjected to percussions and repercussions during each systole, and precipi-

tation of lipoids occurs by mechanical disturbance of the colloidal state of the lipoids in the ground substance.

While precipitation of lipoids, formation of cholesterin crystals, and deposits of calcium occur in atheromatous heart valves just the same as in blood vessels, proliferative changes are absent due to the lack of blood vessels in the ventricular side of the mitral leaflet.

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DYNAMICS OF BLOOD FLOW IN THROMBOANGIITIS OBLITERANS

MILTON LANDOWNE,* M.D.
CHICAGO, ILL.

IN THROMBOANGIITIS obliterans, although changes occur in the veins and about nerves, the essential lesion is an irregular reduction in the luminal diameter of the arteries,[1] and therapy has been largely directed toward relieving the ischemia which results. Vasodilatation is the purpose of many of the methods used in treatment. It is held[2-4] that by vasodilation the development of a collateral circulation will be augmented, and the nutrition of the limb improved. In addition, it has been thought[2-7] that an increase in the amount of blood flowing to the limb may be brought about by these vasodilating mechanisms. It might be possible, therefore, by measuring the volume flow of blood to such limbs, to learn what methods relieve spasm, encourage regressions of the lesion, or generally increase the blood flow to the region. Obviously, certain important information would not be obtained by measuring blood flow. No evidence would be elicited concerning the state of nutrition of any local part or the distribution of the blood flow within the limb. An area of skin which is potentially gangrenous may receive an increased supply of blood, and heal completely at the expense of the circulation elsewhere within the limb (muscles, A-V shunts, etc.), and at no time need the *total* supply of blood to the limb have been increased. Dilatation of vessels in response to a stimulus might not be detected unless this were associated with an increase in flow. Simultaneous vasoconstriction in one area and vasodilatation in another would provide this situation, and it is one of the purposes of this communication to emphasize that even dilatation alone may not be reflected by increased flow under certain conditions imposed by disease. Therefore, clinical improvement cannot a priori be judged simply from measurements of the blood flow to the resting limb, and, because of the unknown and variable factor of distribution of blood within the limb, might not even be reflected by measurements of the blood flow to the limb after maximal vascular dilatation had been induced.

It is further to be noted that a change in blood flow per minute which may be insignificant by comparison with the sensitivity of the method, or with the magnitude of variations in flow, nevertheless, over a period

From the Cardiovascular Department, Michael Reese Hospital, Chicago.
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*Emanuel Libman Fellow.

of days or months, can provide a total increase in blood supply which may be significant with respect to survival of tissue. To illustrate, an average increase in blood flow of 0.1 c.c. per min. per 100 c.c. of limb would result in one day in an increase of 144 c.c. in the amount of oxygen delivered to each 100 c.c. of limb. Finally, although a change in the effective peripheral resistance is reflected in a change in blood flow, the reverse is true only when cardiac output and blood pressure are constant.

Kunkel and Stead[8] have demonstrated that in thromboangiitis obliterans the "maximal" blood flow (that which results from keeping the temperature of the limb at 43° C. for thirty minutes or more) is reduced, and have presented a general correlation of the values for maximal flow with the presence and severity of symptoms. Abramson, et al.,[9] obtained values in agreement with these. They have recently reported[10] that certain procedures will not increase blood flow. Our own observations are in complete accord with theirs. We have studied the blood flow in the legs of subjects with thromboangiitis obliterans and have investigated the response to temporary arterial occlusion.

METHOD

Blood flow was measured in the leg-foot of resting subjects in the horizontal position by an improved modification[11] of the plethysmographic method of Hewlett and Van Zwaluwenburg.[12] This depends upon the theoretical principal that, if venous return be prevented abruptly (by inflating a cuff about the calf to a level below diastolic, but above venous, pressure), the limb will increase in volume. The initial rate of increase in volume should represent the rate of arterial inflow which was present just before the measurement was made. The foot and lower part of the leg were encased in an air-containing, insulated plethysmograph. A thin, nonconstricting rubber diaphragm was cemented to the leg and stretched over the opening, and this closure was made rigid by a plaster of paris backing. Volume changes were transmitted via a short vertical tube to a counterbalanced celluloid spirometer, damped in a glycerine-water mixture. A long lever wrote in ink on kymograph paper. In this manner, changes in the volume of the portion of limb within the plethysmograph were recorded upon the kymograph. Temperature was recorded. Calibration was carried out by means of a syringe which was connected directly to a side tube. Although the form of the pulse wave was not accurately reproduced, pulsations were visible in the records on normal subjects. These were almost always absent in records from patients with thromboangiitis obliterans or arteriosclerosis obliterans.

A narrow (5 cm.) pneumatic cuff was placed about the leg, just proximal to the plaster seal. When this was abruptly inflated, the spirometer recorded an increase in volume. The initial slope of this rising curve was ascertained by drawing a *"tangent" line*, and was expressed as Θ, = the horizontal distance in millimeters traversed by the kymograph paper for a 4 c.c. increase in volume as measured on curvilinear ordinates. This was converted to blood flow in terms of cubic centimeters per minute per 100 c.c. of limb volume by the following expression:

$$\text{Blood flow} = \frac{400\ S\ R}{V\ \Theta} \text{ c.c./min./100 c.c. limb volume,}$$

where V = limb volume; S = paper speed in mm./min.; R = calibration factor; Θ = tangent in mm./4 c.c. For a given experiment, at each speed used, $\frac{400\ S\ R}{V}$ is a constant. Each measure-

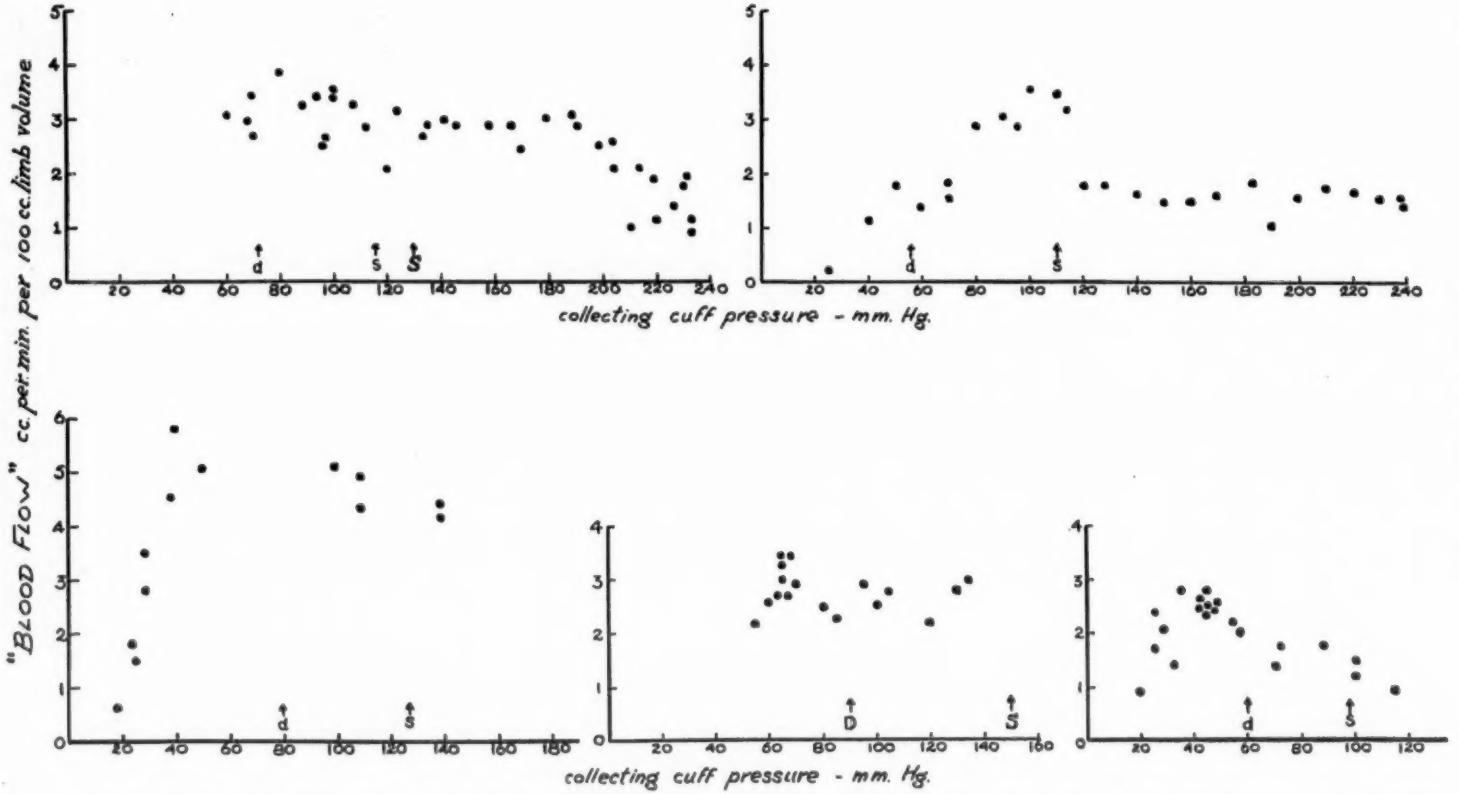

Fig. 1.—The effect of varying "collecting cuff" pressure upon the recorded blood flow in the foot-leg of subjects with thromboangiitis obliterans. The systolic and diastolic blood pressures in the popliteal artery are indicated by *S* and *D*, or in the brachial artery by *s* and *d*, respectively, in each case. Discussed in text.

ment of flow may be completed within about three to seven seconds, and repeated as often as every ten or fifteen seconds.

The validity of this method depends upon (a) the completeness of the venous occlusion, (b) the absence of initial obstruction to arterial inflow, (c) the distensibility of the vascular system and of the limb, and (d), in any system, the ability of the recording system to register rates of change in volume accurately. Many workers, as well as ourselves, have studied the limitations of the method.[8, 9, 11] These studies have indicated that consistent results may be obtained in normal persons. No insistance is made by us as to the degree of absolute accuracy of these values. Conformity, sensitivity, and predictable behavior appear to indicate that the apparatus is suitable for measuring blood flow to distal parts of normal extremities.

It was necessary, however, to ascertain whether the method is applicable to diseased limbs. With reference to the first three points above: (a) In thromboangiitis obliterans, veins with thickened walls might be less easily occluded by the cuff pressures used, and collateral venous flow may not be as easily accessible to occlusion by the cuff pressure. (b) Small collateral arteries, with thinner walls and under lower pressures, may be occluded, at least in part, by the application of a collecting cuff. (c) The walls of thickened veins are less distensible and venous space is diminished. Tissues are more rigid and less distensible. Venous stagnation is not uncommon.

The following observations were made upon the extent to which these factors interfered with the use of the method. The increase in volume which occurred upon application of the collecting cuff to subjects with thromboangiitis obliterans was as prompt as in normal subjects. It continued, without appreciable decrease in slope, as long or longer. The resting rate of blood flow was of the same order of magnitude as in the normal subject. As the pressure used in the collecting cuff was varied, the recorded blood flow was greatest over a certain range (Fig. 1), just as in the normal. The optimal pressures which were required varied from patient to patient, and ranged from 30 mm. upward. As the cuff pressure was increased above the diastolic level, the recorded blood flow did not always decrease. Pressures above the estimated systolic pressure in the popliteal artery still resulted, in some subjects, in sizable recorded flows. This also was noted in normal subjects, but it apparently required higher pressures in the narrow cuff about the calf to reduce or abolish arterial inflow (Fig. 1). This was true also when a wide cuff was applied about the thigh for the purpose of occluding inflow; a slow volume increase of the foot-leg was noted after inflation of such a cuff to well above brachial systolic pressure (200 to 300 mm. Hg). Inflation of the lower cuff to 50 to 70 mm. Hg would then reveal the magnitude of this slight inflow of blood.

These observations would indicate (1) that venous obstruction produced by inflation of the collecting cuff was as adequate in patients with thromboangiitis obliterans as in the normal subject, (2) that arterial inflow was not significantly obstructed during measurements, and (3) that it was more difficult to completely occlude arterial inflow by pressure cuffs.

The distensibility of vessels also appears adequate for the application of the method, for the volume curve rises steadily. It remains possible that, if the limb was previously congested, such congestion would interfere sooner with initial inflow of blood when the cuff was applied to obstruct venous return. This would cause the recorded flow to be erroneously small. The actual flow might be low in such a congested limb, but the degree of reduction would be exaggerated by any such inadequacy of the method. To test this, congestion of the leg was produced deliberately, and to a degree greater than that which occurred during the course of any experiment. Blood flow was measured repeatedly after release of congestion, and was never less than control values for more than thirty seconds; the average

duration of any decrease was less than fifteen seconds (Fig. 2*A*). Hence it is concluded that, as in normal limbs, congestion may result in reduced flow and/or introduce an error, but, if any such artifact is present, it does not persist longer than thirty seconds after release of the congesting force. The relevant data are presented with the experiments to which they are pertinent.

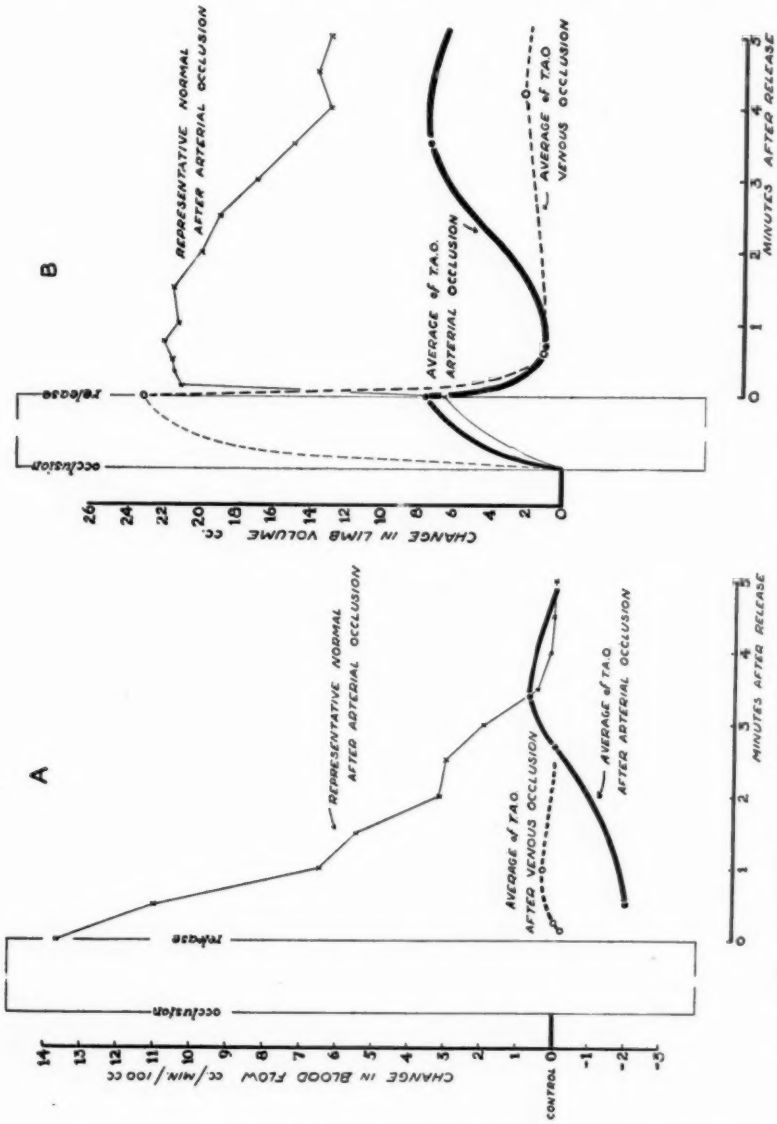

Fig. 2.—The change in blood flow after the release of arterial occlusion (*A*), and the change in volume of the limb during and after the same procedure (*B*). The heavy line indicates the average of changes after release of eighty-nine arterial occlusions (average duration of occlusion, 7.9 minutes) (see Table I), and the broken line indicates the average of changes after release of deliberate congestion produced by twelve venous occlusions (average duration, four minutes) in subjects with thromboangiitis obliterans (T.A.O.). The light line indicates a representative experiment on a normal subject (arterial occlusion of six minutes).[11] Actual flows or volumes are not shown on this chart; only the change in flows and volumes are shown. Discussed in text.

Experiments were carried out (as on normal subjects[11]) in the following manner. The patient rested in bed, with the leg (usually the left) within 10 cm. of heart level. After thirty minutes a series of resting flow measurements were made, usually at intervals of thirty seconds, and over a period of five to fifteen minutes. The effect of arterial occlusion upon volume and flow was observed by abruptly inflating (from a pressure tank) a 16 cm. cuff about the thigh to 200 to 350 mm.

Hg, and maintaining this occluding pressure for varying periods of time. Any incompleteness of occlusion was revealed by an increasing limb volume during the period of occlusion. Upon release of the occluding cuff, repeated measurements of flow were made at intervals of fifteen to thirty seconds, and then less frequently for two to fifteen minutes. Occlusion and release were repeated, usually for the same or different periods, one or more times. In this manner the effect of varying occlusion pressure or occlusion time could be related to the initial flow caused by release, the maximal flow observed, the changes in flow and their duration, the changes in limb volume, and visual and subjective notations. In several experiments, heart rates were recorded.

The effect of heat, either alone or in combination with occlusion, was also studied. Heating to 40 to 45° C. for thirty minutes preceding and between measurements was accomplished by a thermostatically controlled hot-air blower, which was detached during measurements. In these experiments no observations on basal volume change were made. The volume changes caused by temperature variation during the three to seven seconds which were necessary for each measurement were not significant, as was demonstrated by observing the volume change over an equal period preceding and following the measurement.

Observations during forty-six experimental periods, comprising measurements of blood flow before, during, and after eighty-nine trials of arterial and twelve of venous occlusion of the leg in seven cases of thromboangiitis obliterans are summarized in Table I. The subjects were men between the ages of 32 and 54 years. All were ambulatory, coming from home, or hospitalized for ganglionectomy, and had mild to moderate symptoms. No active phlebitis was manifest. Two patients presented trophic lesions, which healed with hospitalization and ganglionectomy, and one had a recently healed lesion.

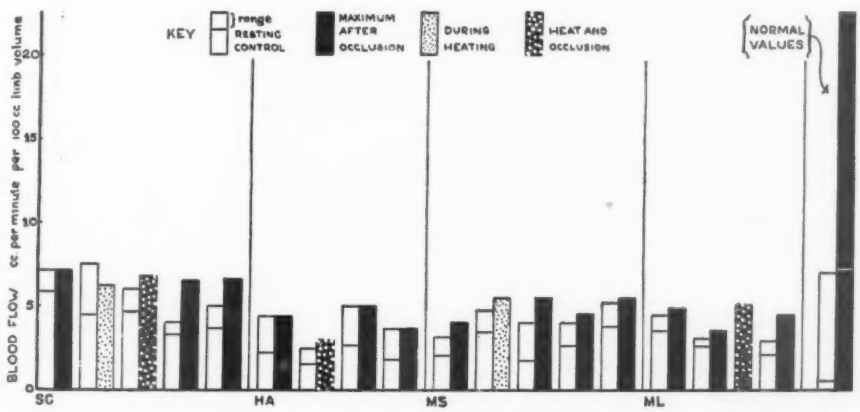

Fig. 3.—Illustrative examples of blood flow in the foot-leg of subjects with thromboangiitis obliterans at rest, and after dilating procedures, as compared with average of values for normal subjects.[11] Discussed in text.

The resting flows ranged from 1.1 to 7.5 c.c./min./100 c.c. of limb volume (Fig. 3). The minimum range in each experimental period was 0.4 c.c., the maximum, 3.2 c.c. In an attempt to increase the blood flow by inducing reactive hyperemia, a cuff about the thigh was inflated to a pressure of 200 to 300 mm. Hg, and this pressure was maintained for one-half to fifteen minutes; the maximum resulting flows ranged from

TABLE I

SUMMARY OF DATA ON BLOOD FLOW IN THE LEG-FOOT OF SUBJECTS WITH THROMBOANGIITIS OBLITERANS

SUBJECT	ALL SUBJECTS	CE	AB	LA	SA	TO	CO	BE
Age of subjects (years)	32-54	41	52	43	50	38	32	54
No. of experimental periods	46	6	10	11	10	3	4	2
No. of trials of occlusion	101	14	20	22	25	7	7	6
BLOOD FLOW								
Resting flow (range) (c.c./min./100 c.c.)	1.1-7.5	1.1-7.5	1.5-5.6	1.3-5.2	1.5-5.6	1.3-3.2	1.8-3.4	2.5-5.7
Resting flow variation in individual experiment (c.c./min./100 c.c.)	0.4-3.2	0.8-3.0	0.7-3.3	0.4-2.6	0.4-2.3	0.5-0.9	0.7-1.2	1.2-3.2
A. Arterial Occlusions								
No. of trials of occlusion	89	14	16	19	22	7	7	4
Duration of occlusions (range in min.)	½-15	2-12	5-15	5-15	½-12	1-8⅓	5-10	5-10
Av. duration of occlusions (min.)	7.9	7.2	10	9.5	7.1	5	8	7.5
Maximum flows after release of occlusions (c.c./min./100 c.c.)	2.5-7.6	3.4-7.6	2.9-5.8	2.8-6.1	2.6-6.3	2.6-3.2	2.7-3.8	5.6-6.6
Greatest maximum increase in flow (c.c./min./100 c.c.)	2.7	2.7	1.8	2.0	2.3	1.3	0.8	2.6
Av. maximum increase in flow (c.c./min./100 c.c.)	0.7	0.4	0.4	0.9	1.0	0.5	0.4	1.8
No. of trials when maximum increase was ≧ 1 c.c.	30	2	3	9	11	2	0	3
≧ 2 c.c.	6	2	0	1	1	0	0	2
< 1 c.c.	59	12	13	10	11	5	7	1
Av. time after release at which maximal increase ≧ 1 c.c. was manifest (min.)	3.4	3.5	5.8	2.8	3.5	4.7	----	1.5
No. of trials when a decrease ≧ 1 c.c. occurred	46	11	9	5	8	6	4	3
No. of trials when a decrease ≧ 1 c.c. lasted ≧ 1 min.	43	11	9	5	7	5	4	2
No. of experimental periods when a decrease ≧ 1 c.c. occurred	29	4	7	4	6	3	3	2
No. of experimental periods when a decrease ≧ 1 c.c. lasted ≧ 1 min.	28	4	7	4	5	3	3	2
Av. magnitude of decreases (all cases) (c.c./min./100 c.c.)	1.8	2.5	1.8	0.6	0.9	1.5	1.1	2.0
Av. duration of any decrease (min.)	2.7	2.6	3.3	2.2	2.6	2.8	3.4	1.1
No. of trials when, after an initial decrease ≧ 1 c.c., an increase occurred	30	2	4	5	8	5	3	3
No. of trials when this increase ≧ 1 c.c.	12	0	1	2	5	2	0	2

B. Venous Occlusions								
No. of trials of occlusion	12	0	4	3	3	0	0	2
Duration of occlusions (range in min.)	1-11	----	1-5	5-11	1-5	----	----	2
Av. duration of occlusions (min.)	4	----	4¼	7⅓	2⅓	----	----	2
Av. magnitude of decrease in flow (c.c./min./100 c.c.)	0.2	----	0.3	0.3	0.9	----	----	0.4
Av. duration of any decrease (min.)	<¼	----	1/30-<½	1/6-½	1/30-¼	----	----	0-½
Av. maximal increase in flow (c.c./min./100 c.c.)	0.3	----	0	0.5	0.4	----	----	0.4
Av. time after release at which maximal increase was manifest (min.)	1	----	----	3⅓	----	----	----	⅔

CHANGE IN LIMB VOLUME

A. Arterial Occlusions								
No. of trials in which volume change was determined	68	3	15	14	18	7	7	4
Av. increase in volume during occlusion (c.c.)	7.6	7	10	5	13	2.5	1.5	10
No. of trials in which decreases in volume occurred after release of occlusion	51	3	15	8	15	6	0	4
Av. extent of decreases in volume (c.c.)	6.7	7	15	2	5.6	7	0	9.4
Av. duration of decreases in volume (min.)	⅔	½	1¼	½	⅝	1½	----	½
No. of trials in which increases in volume occurred	61	3	13	13	14	7	7	4
Av. maximum extent of this increase (primary or secondary) (c.c.)	6.5	11	9	5	4.3	6.5	7	8
Av. time at which maximum increase occurred (min.)	3½	3	6½	3¼	2	4½	1¾	1⅞
B. Venous Occlusions								
No. of trials in which volume change was determined	12	0	4	3	3	0	0	2
Av. increase in volume during occlusion (c.c.)	23	----	30	24	12	----	----	25
No. of trials in which decreases in volume occurred after release of occlusion	12	----	4	3	3	----	----	2
Av. extent of decreases in volume (c.c.)	22	----	27	22	14	----	----	25
Av. duration of decreases in volume (min.)	⅝	----	¾	1¼	½	----	----	⅞
No. of trials in which increases in volume occurred	4	----	0	3	1	----	----	0
Av. maximum extent of this increase	1¼	----	0	4	3½	----	----	0
Av. time at which maximum increase occurred (min.)	4.2	----	----	4	5	----	----	----

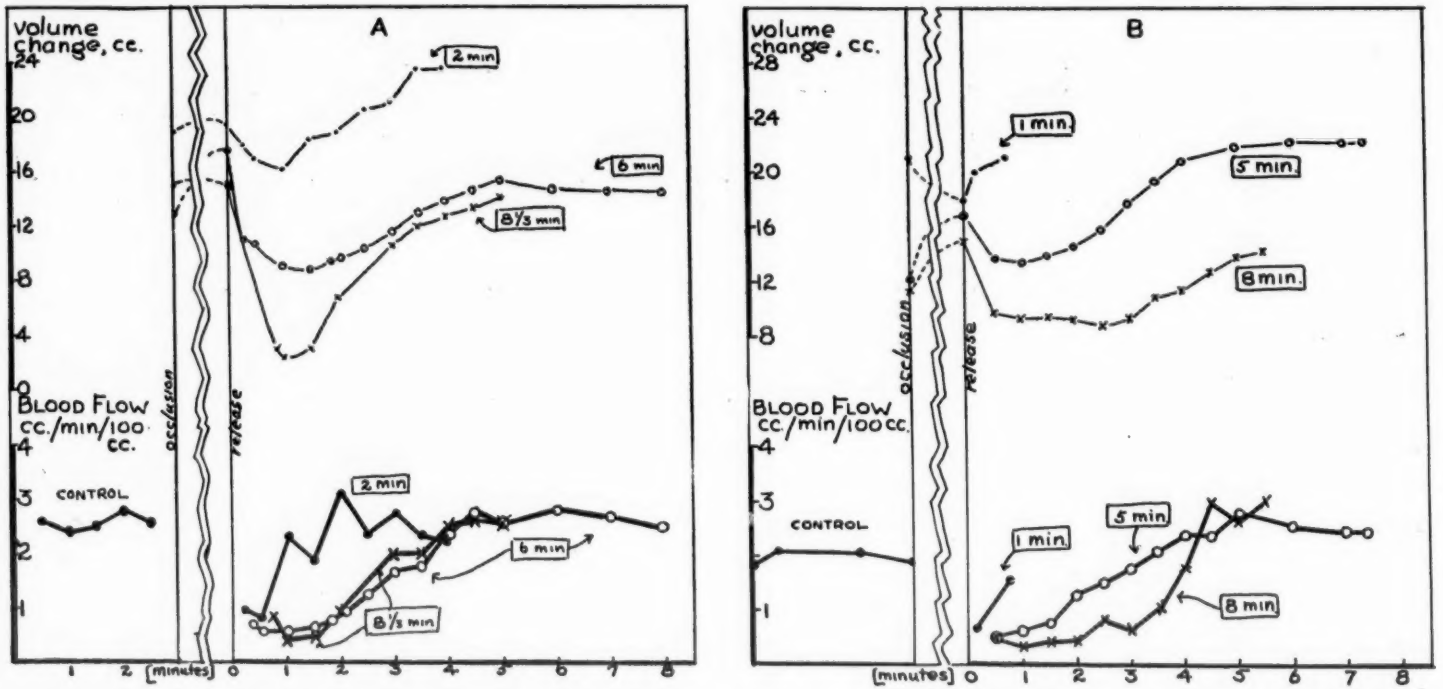

Fig. 4.—The effect of lumbar sympathetic ganglionectomy upon the resting and "maximal" blood flow in the foot-leg of a subject with thromboangiitis obliterans. The resting control flow, the flow after release of arterial occlusions of comparable durations, and the changes in limb volume after the release of these occlusions are shown in *A* prior to, and, in *B*, one week after, lumbar sympathetic ganglionectomy. The duration of the occlusion which preceded each curve is indicated on the several curves. Discussed in text.

2.5 to 7.6 c.c. (Fig. 3). The greatest increase in flow in any case was but 3 c.c. The maximal increase after release was less than 1 c.c. following fifty-nine trials in thirty-six experimental periods, and was equal to, or greater than, 1 c.c. in thirty trials.

In a series of observations on thirteen normals,[11] the resting flows were similar, i.e., 0.5 to 6.0 c.c./min./100 c.c., but the maximal flows after release of arterial occlusion were 7.3 to 22.6 c.c./min./100 c.c. (Fig. 3).

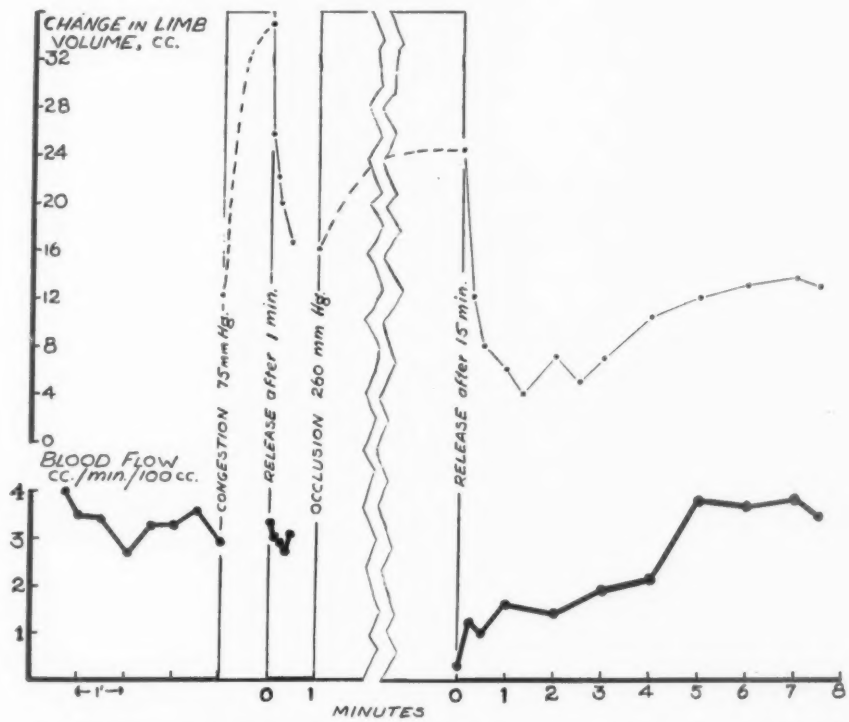

Fig. 5.—Comparison of the effect of congestion (by venous occlusion for one minute) and ischemia (by arterial occlusion for fifteen minutes) upon the blood flow and limb volume of the foot-leg in a subject with thromboangiitis obliterans. Discussed in text.

Heating the limb to evoke maximal dilatation, in ten experiments upon six patients, or combined heating and arterial occlusion, in ten trials in eight experiments on five patients, did not significantly alter the resting level of blood flow.

Lumbar sympathetic ganglionectomy, which was performed on three patients, did not alter significantly either the resting blood flow of the ipsilateral foot-leg nor the response to arterial occlusion, although a distinct increase in skin temperature was noted (observations made about one week after operation) (Fig. 4).

Unexpectedly, we observed (Figs. 2, 4, Table I) that, instead of the immediate increase in flow noted normally (Fig. 2), the release of

arterial occlusion in some cases was followed by a decreased blood flow; the maximum decrease was equal to, or greater than, 1 c.c. in forty-six trials in twenty-nine experimental periods. In thirty of these forty-six trials, a decreased blood flow was present for two minutes or more. The average of the maximal decreases in all cases was 1.8 c.c. The average time after release of the occlusion during which a decrease was manifest was 2.7 minutes.

During occlusion a volume increase sometimes occurred. Deliberate congestion of the limb at the beginning or at the end of the period of occlusion, or without occlusion, which produced a large volume increase (Fig. 5), demonstrated that the factor of congestion did not vary the results for more than thirty seconds after the occlusion had been released. The average maximal decrease in flow caused by deliberate congestion in twelve instances of venous occlusion was 0.2 c.c., and lasted less than fifteen seconds after release of the occlusion (Fig. 2). For purposes of clarification, and to avoid this questionable factor, the calculations of the decrease in flow after release of arterial occlusion without deliberate congestion were based only on measurements which were made thirty seconds or more after release.

The initial decrease in flow after release of arterial occlusion was investigated further in a few experiments. In ten instances, heating the plethysmograph to 40 to 43° C. for at least thirty minutes before, and maintaining this temperature during arterial occlusion did not modify the results significantly. After release of occlusions which averaged 9.4 minutes, the maximal decrease in flow averaged 2.2 c.c., and the decrease persisted for an average time of 2.4 minutes. The response before and after lumbar sympathetic ganglionectomy was also compared in three cases. The average maximal decrease in flow after release of the arterial occlusion (average duration, 7.2 minutes) was 1.2 c.c., and the average duration of any decrease was 1.6 minutes, in ten preoperative trials. One week after the ipsilateral removal of the the second, third, and fourth lumbar sympathetic ganglia, the average of seven trials on these patients indicated an average maximal decrease of 1.8 c.c., and an average duration of any decrease of 2.4 minutes (Fig. 4).

The changes in limb volume after release of arterial occlusion were calculated in sixty-eight instances (Table I). Primary decreases in volume occurred fifty-one times; the maximum of each ranged from 0.5 to 22.5 c.c., averaging 6.7 c.c., at an average time of ⅔ minute after release. In the control group there was an immediate increase in volume, which was sustained (Fig. 2). In the subjects with thromboangiitis obliterans, an increase, delayed in onset, occurred in sixty-one trials. The maximal increase averaged 6.5 c.c. above the lowest volume level—a return just about to the volume at the time of release of the occlusion. The average time after release that the volume regained this level was 4.2 minutes.

In twenty-one trials the heart rate was noted, either by timing ten pulse beats with a stop watch (nine trials), measuring the rate recorded in fifteen seconds on an electrocardiograph (nine trials), or calculating

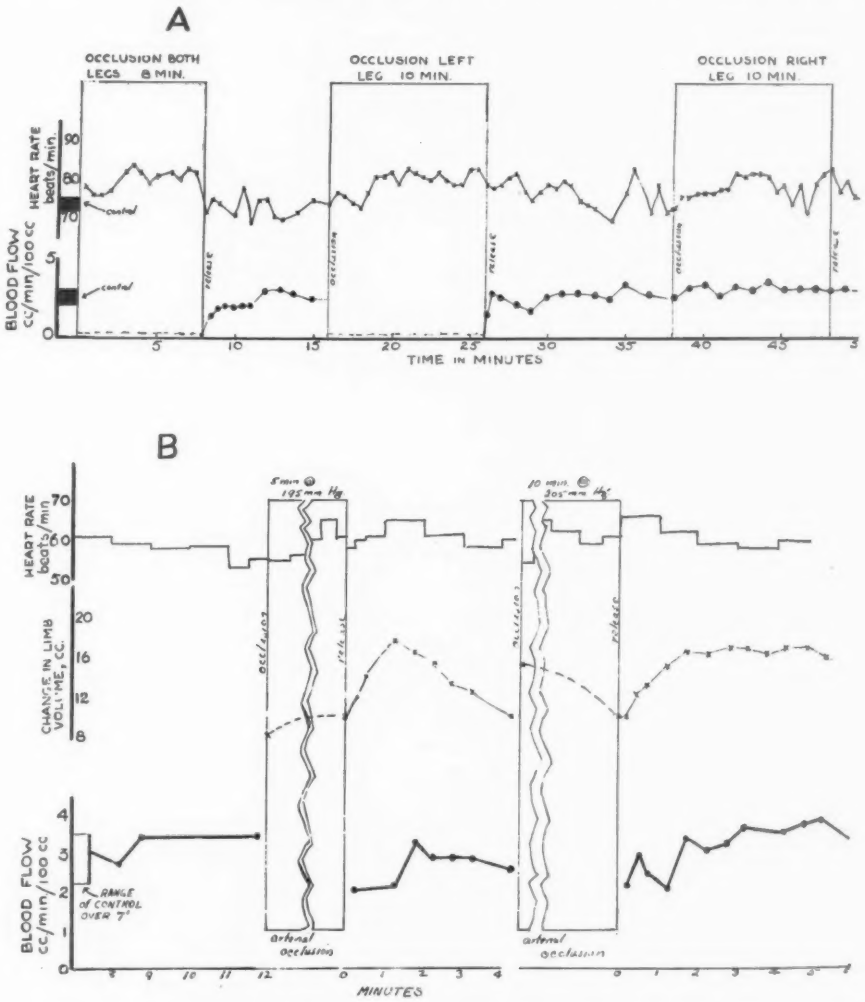

Fig. 6.—*A*. The effect of arterial occlusion of the same and of the contralateral leg upon the blood flow in the left foot-leg, and upon the heart rate, of a subject with thromboangiitis obliterans. *B*. Heart rate, limb volume change, and blood flow, as affected by occlusion and release of arterial circulation to the leg of a subject with thromboangiitis obliterans. Discussed in text.

the rate from the cycle length of each beat (three trials). The occlusions were seven to fifteen minutes in duration (averaging eleven minutes). The change in heart rate upon release of occlusion (Fig. 6) was from −10 to +10 beats/min., averaging +1 beat. In a series of normal subjects[13] the change in rate was +7 to +35, averaging +20 beats/min.

DISCUSSION

The number of patients whom we studied is too small to warrant an attempt to establish a correlation of resting or maximal flows with the clinical manifestations. The results are comparable to those of Kunkel and Stead,[8] for our results fit into the range of maximal blood flow indicated by these authors to correspond with the severity of the disease. In general, the slight increases in flow which occurred in response to vasodilating procedures were in the milder cases. The larger initial decrease in flow after release of arterial occlusion occurred in the more severe cases. Observations over control and therapeutic periods totaling three to ten months did not reveal striking alterations in resting and/or maximal flows in the cases studied, or with therapy used, although various degrees of clinical improvement, objective as well as subjective, were noted.

The resting values obtained by us are of the same order of magnitude as the "maximal" values. In other words, arterial occlusion or heat, when used as a dilating agent, did not effect any significant augmentation in recorded blood flow in the patients with thromboangiitis obliterans whom we studied. These agents induce "maximal" dilating mechanisms in the normal subject.

The absence of any comparable cardiac acceleration or limb volume increase after release of arterial occlusion corroborates the observations that the blood flow is not increased.[13]

These results indicate that the procedures which were used did not significantly reduce the effective peripheral resistance in these subjects. To explain this we can postulate that, *in spite of widespread dilatation of smaller vessels, the fixed narrowing of the larger vessels (arteries) offers proportionately so much resistance that the more peripheral dilatation does not effectively reduce the total resistance to flow.*

In order to understand how this last mechanism operates it is important that several considerations be presented. In any vascular segment, some resistance to the movement of blood is encountered at every point along the vascular tree. The distribution of this resistance is not uniform. Normally it is predominantly located in the arterioles, just before the smallest vessels. Because of this distribution, the mean blood pressure in the limb vessels falls but little until the small vessels are encountered. Here, over the relatively short distance from smallest arteries to capillaries, a fall in pressure of 50 to 80 mm. Hg occurs.[14]

When the lumen of any vessel is narrowed, resistance to flow is increased. The factors which govern the precise relationship of frictional loss to the vessel diameter are complex.[15] As a crude approximation for either laminar or turbulent flow, this resistance varies inversely with at least the third power of the radius. Distortions and lengthening of the vascular pathway also increase resistance. When the lumen of a vessel is sufficiently narrowed, as by arteritis, atheroma, etc., the

increased resistance of the large vessels may become a predominant proportion of the total vascular resistance. In such a case the gradient of pressure would fall steeply in these narrowed regions. If all the resistance of the distal peripheral vessels could be removed, as would

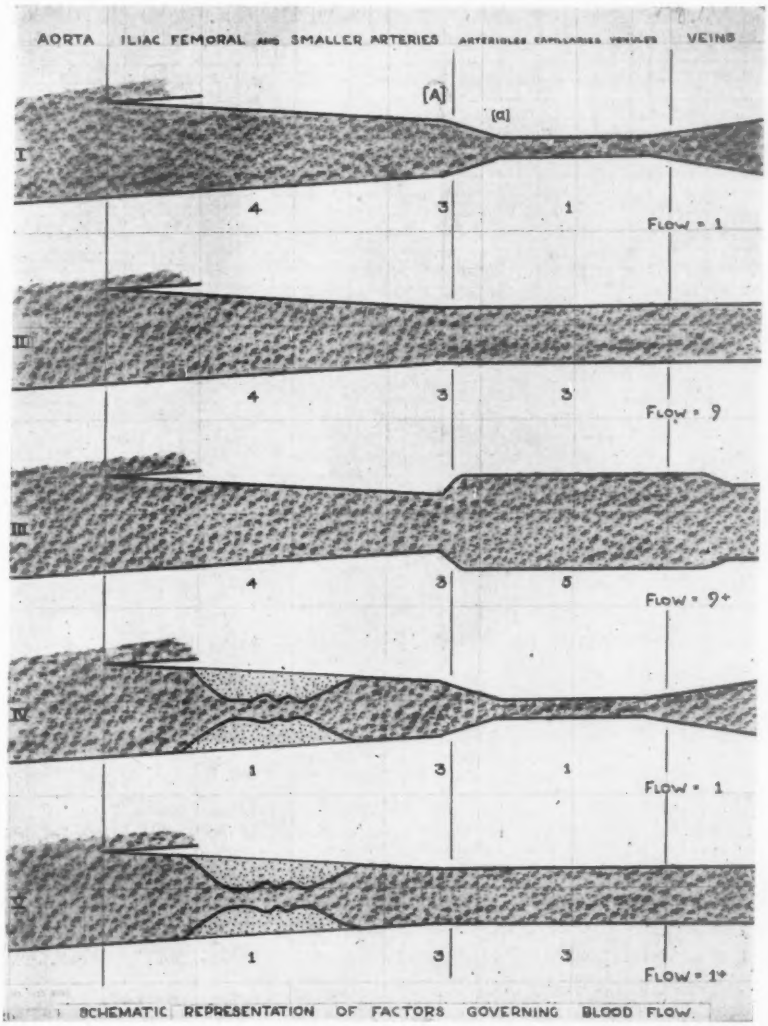

Fig. 7.—Schematic representation of some factors governing blood flow. *I*, *II*, and *III* represent degrees of peripheral vascular dilatation in the normal, and *IV* and *V* represent states similar to *I* and *II* in thromboangiitis obliterans. The proportional radii of each vascular segment are indicated by the numbers under each diagram. The relative flow is suggested by the figure to the right of each diagram. Discussed in text.

occur upon amputating the leg, the initial escape of blood would not be as large as in a normal limb. The amount of this initial flow would depend (just as in the normal) upon the caliber of the opened vessels and the pressure within them. The initial escape would represent the maximal blood flow which could have been supplied to the tissues of

that leg. Although constriction of peripheral vessels would have reduced this flow, dilatation could not have increased it beyond this maximal value (Fig. 7 *IV* and *V*).

It follows, therefore, that, when progressive dilatation of small vessels occurs, a point may be attained beyond which further dilatation is not attended by an appreciable increase in blood flow. This would mean that the size of some proximal vessel is now the factor which limits the magnitude of flow. This, for instance, may be of importance when reactive hyperemia after release of arterial occlusion fails to increase further the volume of blood flow in a normal limb whose skin vessels have been previously dilated by heat[11] (Fig. 7 *I*, *II*, and *III*).

In thromboangiitis obliterans, the narrowing of the arterial lumen (whether entirely or only partially organic) thus eventually determines the maximum amount of blood which can be delivered to the tissues at a given arterial pressure. Beyond this, the state of the peripheral vessels may regulate this flow, reduce it, or distribute it, but cannot increase it. As blood flow is further restricted, a point is reached at which ischemia sets in, at first only when the demand for blood exceeds normal, e.g., during exercise; but, as the disease progresses, the limb at rest may come to require all the blood that the major supplying vessels can transmit. At this point, the peripheral vessels may be in a normal state of activity, or, and this is more likely, they may be dilated.[1, 16] In either event, the impediment to flow is located largely in the major vessels, instead of in the small ones. Finally, with advanced disease, even the minimal normal flow in the resting extremity cannot be forced past the arterial obstruction, and nutrition becomes insufficient to meet the needs of the tissues.

In short, the concept which fits the observations made by us may be summarized as follows: The resting blood flow in limbs affected with thromboangiitis obliterans may be normal, except in severe cases. Dilatation of peripheral vessels will result in an increase in flow only up to the limits imposed by the narrowed arterial lumina. Although in early cases this may permit a significant increase, in manifest cases (in which symptoms of insufficient circulation are evoked by a demand for increased blood), no significant augmentation of blood flow will follow peripheral dilatation.

However, it may be argued that these dilating procedures failed to produce peripheral vasodilatation in our patients, or that any dilatation produced in part of the limb vessel is neutralized by a concomitant and equal vasoconstriction in other parts. This would occur if spasm* were present and unrelieved by the dilating procedure, or if the vessels themselves responded in an abnormal manner.

*Spasm is considered here to represent an undue or disadvantageous degree of vasoconstriction, leading to a reduced blood flow. Vasoconstriction may be present in the diseased limb,[18] and serves to divert the limited blood supply to those regions with the greater demand for blood. General dilatation of peripheral vessels may lessen this advantageous redistribution, and, if more blood is diverted to the skin, the skin temperature may rise even when the total flow to the limb is unchanged. This is not to be considered as spasm, and, therefore, caution must be applied in interpreting skin temperature observations.

It has generally been assumed that the procedures which we used (heat, ischemia, and sympathectomy) abolish vasoconstrictor stimuli, either local or of reflex origin.[17] Increased irritability of the contractile elements of blood vessels in the presence of a defective circulation has been suggested[20-22] from studies of depletion of circulation in animals, of the production of Bier's spots in man, and on vasospastic disorders.[22]

It is conceivable, for example, that a given degree of reduction in oxygen tension may give rise to contraction of an abnormal muscle preparation, although, under normal circumstances, it produces relaxation. The same stimulus may evoke a different response when the condition of the tissue or its environment is altered. Morphologically, little or no alteration has been described in the smallest vessels[1, 19, 23, 24] in thromboangiitis obliterans. This does not mean that physiologic abnormalities may not exist. However, as shown in skin areas by temperature, color, and microscopic observations, local dilator and constrictor agents appear to elicit responses in the normal direction.[18]

Buerger has stated,[1] (page 74) "Vaso-constriction and even vasodilatation are usual and common sequences of obstructive anemia or ischemia.

(Page 240) "Too much emphasis cannot be laid on the fact, however, that most of the objective symptoms regarded by many authors as of neurotic foundation, are merely hydrostatic and compensatory phenomena, although . . . independent vasomotor disturbances may be concomitant . . .

(Page 247) "The conclusion is warranted that the finer vessels are still able to respond, and are not wholly inert and paralytic."

We consider, therefore, that the primary factor limiting the maximal blood flow in our cases of thromboangiitis obliterans was not failure to dilate the small vessels, but the narrowed caliber of the major vessels—the involved arteries—so that, even with peripheral vascular dilatation, the supply of blood to the part was restricted. In any given case this is amenable to investigation by measuring flow before and after dilatation of peripheral vessels is actually produced by a suitable method.

The fact that there is an initial decrease in flow after release of arterial occlusion lends support to the consideration that there may not be an unqualified dilatation in response to ischemia in the limb vessels. Whatever the origin of this decrease, our evidence indicates that it is not abolished by heat or sympathectomy. Therefore, it is to be postulated that this decrease may be evoked by a constrictive response of the peripheral vessels, or of peripheral axons, resulting from deprivation of the mechanical or chemical stimulus of circulating blood; or it may follow direct major vessel or local neuraxon stimulation produced by the occluding pressure of the thigh cuff on the underlying arteries or nerves. The fact that peripheral heat does not reverse this response suggests perhaps that the central rather than the peripheral vessels are con-

cerned. The response seems to be evoked more definitely by longer periods of occlusion (Fig. 8) and is dissipated by re-establishment of circulation. The response may not be peculiar to this disease. It may, in fact, occur in normal subjects. For example, if it is in response to the pressure applied to the major artery, resulting in a narrowing due to local spasm, this may be of a degree which, in a normal vessel, will not significantly increase the total resistance of the hyperemic limb. The same amount of circumferential shortening of muscle fibers may effect an appreciable increase in total resistance in an already narrowed vessel. We have, however, no evidence that this is the case in the normal subject. The mechanism of the initial decrease in flow may be related to that underlying the production of Bier's "white spots" and "ischemic patching."[25] Rous and Gilding,[21] Krogh,[26] Wolf,[27] and Lewis[28] have contributed evidence that these areas of paling occur with prolonged ischemia. Several of the earlier authors have suggested the unsupported hypothesis that asphyxial blood may cause constriction before dilatation.[29]

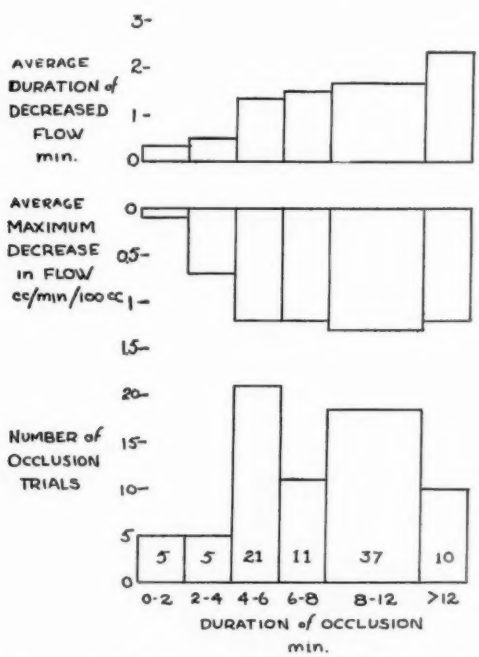

Fig. 8.—Chart correlating the duration of prior arterial occlusion with the magnitude and duration of the decrease in blood flow after release of the occlusion (eighty-nine trials in seven subjects with thromboangiitis obliterans). Discussed in text.

SUMMARY

The resting blood flow in the horizontal position in the foot-leg of seven subjects with moderately advanced thromboangiitis obliterans was found to be within normal limits, as measured by the plethysmographic method.

The release of arterial occlusion in the thigh resulted in no significant increase in blood flow. No initial increase in limb volume and no significant cardiac acceleration followed the release of arterial occlusion in these subjects.

Heat or lumbar sympathetic ganglionectomy, alone or in conjunction with arterial occlusion, was no more effective in increasing the volume of blood flow than was simple arterial occlusion.

After the release of arterial occlusion, an initial decrease in blood flow was manifest. This was not prevented by local heat or by sympathetic ganglionectomy.

CONCLUSIONS

The maximal volume flow of blood in the foot-leg of the subjects with thromboangiitis obliterans whom we studied, consequent to the dilating procedures which were used, was determined largely by the narrowed arterial lumen produced by this disease. This maximum flow was less than that observed in normal persons. It may be reduced to the level of flow with which the normal limb is supplied at rest, or below this level. The distribution of the blood flow to the various parts of the foot-leg is not ascertained by measuring the total volume of inflow into the foot-leg.

Although there is no evidence to indicate that the dilating procedures which were used did not produce dilatation of the small vessels, it is possible that these procedures may evoke abnormal responses in this disease, both qualitatively and quantitatively.

The initial decrease in blood flow consequent to release of arterial occlusion may be caused by the above factor, by a peripheral vasoconstrictor effect of the ischemia, or, most likely, by a local constrictive response of the major vessels.

Since these last two factors may be active in the normal subject, this constrictive response need not of necessity be caused by thromboangiitis obliterans, but at least it becomes manifest in this disease.

The author acknowledges his indebtedness to Dr. L. N. Katz for his guidance. He is obliged to Dr. S. Perlow for permission to study his private patients and patients from the peripheral vascular clinic. He is very grateful, also, for the cooperation of these patients.

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DISSECTING ANEURYSM OF THE AORTA

CLAYTON D. MOTE, M.D., AND JESSE L. CARR, M.D.
SAN FRANCISCO, CALIF.

MORGAGNI[1] in 1760 first described a dissecting aneurysm of the aorta; he saw it "coming out under the external coats of the artery first by drawing it from the internal coats and then by raising it as a large kind of ecchymosis." Maunoir[2] in 1802 clearly described the mechanism of dissection by blood, and Laennec[3] in 1826 first used the term "aneurysm dissequant." Peacock[4] reported nineteen cases in 1843 to which he added sixty-one in 1863. Further excellent reviews and case reports were contributed more recently by Crowell,[5] Moosberger,[6] Wood, Pendergrass, and Ostrum,[7] Etling[8] and others. Gager[9] in 1928 and Shennan[10] in 1934 reported large series of cases. Because of this extensive literature, dissecting aneurysm of the aorta is today regarded as a rather common disease, and single cases are not especially noteworthy unless they present some unusual or interesting features.

In a five-year period, from 1933 to 1937, autopsies were done in sixty cases of dissecting aneurysm at the San Francisco Coroner's Office. An analysis of this volume of material is presented in this report. In addition are given the case reports of four patients with the antemortem diagnosis of dissecting aortic aneurysm. The second patient in this group was carried through pregnancy after the diagnosis had been made.

In 8,438 autopsies done at the San Francisco Coroner's Office during the five-year period upon which this report is based, dissecting aneurysm was found sixty times, or in 0.7 per cent. After deducting 3,099 cases of violent death, we find sixty instances of dissecting aneurysm in 5,339 cases, or 1.1 per cent. It is interesting to note that the incidence of ruptured heart as a cause of death in cases examined at the Coroner's Office is approximately the same, or 1.5 per cent.

The incidence of dissecting aneurysm as found in the Coroner's Office and as taken from hospital records varies considerably.

The higher incidence in coroners' records as compared to hospital records perhaps is explained partly by the fact that dissecting aneurysm of the aorta often occurs in patients who have had no previous symptoms of disease and who die suddenly.

From the Department of Medicine and the Department of Pathology, University of California Medical School, and the San Francisco Coroner's Office, San Francisco.
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TABLE I

COMPARATIVE INCIDENCE OF DISSECTING ANEURYSM

	NO. OF AUTOPSIES	CASES	%
Shannon	1,922 in 24 years	11	0.56
Stanford	3,000 in 30 years	3	0.10
University of California	693 in 5 years	2	0.28
San Francisco Hospital	1,746 in 5 years	4	0.23
San Francisco Coroner's Office	8,438 in 5 years	60	0.7
(Nonviolent death)	5,339 in 5 years		1.1

The age, sex, cause of death, relation of exertion as known to the onset of the dissection are tabulated in Table II.

TABLE II

Sex		*Duration of Life in 60 Cases*	
Male	52	Found dead	18
Average age	58	Dead in 24 hours	39
Female	8	Dead in one month	58
Average age	63		
Cause of Death		*History of Exertion*	
External rupture	57	Severe	9
(Intrapericardial with tamponade 40)		Ordinary work	7
		At stool	1
Heart failure	1	Swimming	1
Obstruction of superior vena cava	1	External trauma	0*
Rupture of associated aneurysm	1		

*A total of 3,099 cases of violent death in 9,438 autopsies showed no evidence of dissecting aneurysm.

Because of the suddenness of death and the fact that these patients have not been attended, the clinical records and observations are often scant and unreliable. Therefore, when the clinical findings in the sixty cases of dissecting aneurysm are evaluated, it should be borne in mind that, although all the available material has been assembled, many details may be lacking.

Physicians attended the patients in only twenty-six cases of the series. The antemortem diagnoses made in these cases are given in Table III.

TABLE III

Cardiac conditions (heart failure, myocarditis, cardiac asthma, arteriosclerotic heart disease)	12
Coronary occlusion	2
Cerebral hemorrhage	1
Carcinoma of the stomach, hemorrhage	1
Aneurysm of the aorta	1
Chronic nephritis	1
Acute indigestion	1
Mediastinal tumor	1
Senility	1
Pulmonary hemorrhage	1
Lumbago	1
Dissecting aneurysm of the aorta	3

The clinical findings as reported in twenty-six cases of dissecting aneurysm that were seen antemortem by physicians are given in Table IV.

TABLE IV

Cardiac enlargement	10	Fever	4
Normal rhythm	25	Cough	3
Auricular flutter	1	Pleural fluid	2
Abnormal aortic sounds and murmurs	7	Basal râles	8
		Hemoptysis	2
Aortic thrill	1	Albuminuria	8
Aortic regurgitation	2	Micr. hematuria	4
Elevated blood pressure	7	Gross hematuria	1
Normal blood pressure	19	Leucocytosis	4
Aortic dullness	2	Neurologic symptoms (i.e., reflex changes and weakness)	4
Enlarged neck veins	2		
Occlusion of iliac arteries	2		

Electrocardiograms were taken in only two cases; in one, left axis deviation and flattened diphasic T-waves in Lead I occurred while in the other, that of a patient who was digitalized, auricular flutter with partial heart block was found. A study of the literature shows that marked electrocardiographic changes or notable variations from day to day do not occur in cases of dissecting aneurysm of the aorta. Roentgenograms were obtained in four cases. In the first case they showed no abnormality; in the second, cardiac enlargement with dilatation of the ascending and transverse arches of the aorta and pulmonary congestion were noted; in the third, the heart was enlarged and the thoracic aorta showed diffuse widening and elongation; in the fourth, there were two fusiform dilatations of the thoracic aorta, one on the ascending and one on the proximal descending aorta; the left ventricle was enlarged.

DIAGNOSIS

The number of patients in whom diagnosis of dissecting aneurysm of the aorta is made during lifetime is small because the condition is rare and because death often occurs before satisfactory observations can be made. Its presence is often overlooked in spite of our gradually accruing knowledge of the condition. If the aneurysm is recognized, proper supportive measures may be applied, and errors in diagnosis, which have led to operations such as exploratory laparotomy or other courses of treatment equally harmful, may be avoided.

In some cases the differentiation of a dissecting from a saccular aneurysm due to syphilis may be made from the history. The onset of the saccular aneurysm is usually gradual although its presence may be made known by acute symptoms. Generally, however, the saccular aneurysm is not acutely incapacitating, and it is usually due to syphilis. The roentgenograms of diffuse aortic aneurysm are often similar to those of the dissecting type.

Pain is one of the most constant findings in dissecting aneurysm, but it may be absent in some cases. It may vary from slight to excruciating in type. It is frequently described as "ripping" or "tearing" in

character. It may be persistent during the progression of the dissection, or it may be intermittent and less intense as the process becomes stationary. The location of the pain depends on the portion of the aorta in which the dissection is occurring. It may be in the chest, in the intrascapular region, in the lumbar region, in the abdomen, in the sacral region, or in the hips. In some cases the progress of the dissection may be observed by the changing location of the pain.

As the dissection progresses, intramural rupture of the vessels which arise in the aorta occurs. The dissection may extend also along the medial coats of these vessels. In either case there are obstructive signs in the peripheral circulation as a result of interference with the lumen of these vessels at the point of exit from the aorta. Neurologic manifestations are frequently seen. One of the most frequent symptoms is weakness of the lower extremities due to involvement of the branches of the aorta which supply the lower portion of the spinal cord.[13] The paresis of the legs may be either transient or persistent. Urinary retention may occur due to sphincter disturbances. Syncope, convulsions, coma, and hemiplegia may result from interference with the cerebral circulation.

Any of the palpable peripheral vessels may be involved and at times difficulty in differentiation from an embolic or thrombotic occlusion of the vessel might arise, particularly when either iliac artery becomes occluded from a dissecting aneurysm of the abdominal aorta. The location of pain is an important factor in distinguishing between an embolic occlusion of the iliac artery and an occlusion due to a dissecting aneurysm. Embolic and thrombotic occlusion of the iliac arteries is accompanied by sudden severe pain which usually is in the calves of the legs and is due to ischemia of the leg muscles. In dissecting aneurysm of the abdominal aorta, the pain is usually sudden and acute in onset, is located in the abdomen or the back, and may radiate into the hips. The pain in this instance originates in the aortic wall and probably is due to splitting of the aortic coats. As the dissection proceeds and obstruction of the iliac arteries takes place, ischemic pain similar to that found in embolic or thrombotic occlusion of the arteries may occur in the lower extremities. In order to distinguish between these two conditions, emphasis is placed on the initial location of pain in dissecting aneurysm. When dissection occurs in the ascending arch, the pain is in the chest and back with perhaps occlusive signs in the arm or in the carotids accompanied by cerebral symptoms. The initial appearance of pain in the chest and the back is the important point in differentiation from embolism or thrombosis.

The pain in dissecting aneurysm may simulate and be indistinguishable from that found in coronary thrombosis. Of great help in differentiating these two conditions may be the almost simultaneous appearance of pain and peripheral vascular signs of an occlusive nature in dissecting aneurysm. There often are objective differences in the

carotid, brachial, radial, or femoral arteries, or such visceral manifestations as are seen in renal infarction with hematuria. Embolic phenomena in coronary thrombosis do not occur until sufficient time has elapsed for the formation of a myocardial infarct and a mural thrombus.

The sudden appearance of aortic murmurs and, not infrequently, of aortic regurgitation is of great diagnostic value. In most instances no actual involvement of the aortic valves is found. The insufficiency apparently is due to dilatation of the aortic ring as a result of the dissection of blood through the medial coat at the root of the aorta. As the blood approaches the aortic cusps, it interferes with the muscular elements that support the aortic ring which subsequently dilates.

PROGNOSIS

The prognosis in dissecting aneurysm of the aorta is grave. Various estimates of survival have been made. Crowell[5] stated that 20 per cent of the patients have a chance to survive the initial episode. Weiss[14] recently estimated that one in ten patients has a good chance to recover with development of a "healed" aneurysm. Thirty-eight of Shennan's[10] 300 patients lived for two to thirty years. In our series of sixty cases, only two patients lived longer than a month after onset. The patient in Case 2 of the special case reports lived for two years and ten months after onset.

PATHOGENESIS

Although the opinions generally expressed in the literature as to the pathogenesis of the lesion may vary somewhat, they agree in certain details. First, it is held that the medial wall is weakened by a sequence of destruction and repair. The repair process consists of a light fibrosis with subsequent deposition of cholesterin, fatty acid crystals, and calcium which are common to an arteriosclerotic process and unlike the strong, fibrous, vascularized tissue seen in syphilis. Second, the occurrence of a sudden rise in blood pressure is assumed. Third, it is held that a tear in the intima of the aorta may or may not occur. In the fifty-six cases of this series in which the intimal tear was described, the position was as follows: ascending aorta in forty-two, arch of the aorta in eleven, descending aorta just below the arch in three. In seven of the eleven cases of intimal tears in the arch, the aorta showed evidences of syphilis. In one case, two separate intimal ruptures were observed in the ascending portion of the arch, and in another the tear started in an atheromatous ulcer. The tears were from 2 cm. to 10 cm. in length and varied in shape, being crescentic, V-shaped, longitudinal, oblique, irregular, or transverse. The shape of the tear apparently had no relation to the extent of dissection or the condition of the intima, but simply took on the conformation of the weak medial portion when the dissection began. The external shape of the dissection between the layers of the aortic

wall was sheathlike in fifty, fusiform in six, and saccular in four cases. In most cases the separation of the coats of the aortic wall with extravasated blood extended from one-third to two-thirds of the aortic circumference. In one case, the aorta was completely encircled with blood, forming a so-called "tube-within-a-tube" arrangement.

Because of the common association of aneurysm of the aorta with syphilis, the question has been raised as to the relationship of syphilis to dissecting aneurysm. According to reports in the literature, aneurysm of the saccular type without dissection is due to syphilis in from 25 to 75 per cent of the cases, while most cases of dissecting aneurysm are due to arteriosclerosis uncomplicated by syphilis and only a small number to syphilis alone. In only two of the series of sixty cases of dissecting aneurysm was the diagnosis of syphilis made antemortem. In eleven cases, however, or 18 per cent, the presence of syphilis was proved post mortem either serologically or by tissue section. The cytologic criteria for the presence of syphilis were the microscopic pictures of perivascular infiltration of lymphocytes about the vasa vasorum, of scarring and vascularization of the media, and of mural fibrosis and wrinkling of the intima. According to these figures, the incidence of syphilis is somewhat higher than that found by Shennan, who reported its presence in 10 per cent of his cases of dissecting aneurysm. Arteriosclerosis was found in fifty-seven cases of the series. In most cases the arteriosclerosis of the aorta was far advanced, and generalized arteriosclerosis also was present. Nine of the eleven cases in which syphilis occurred presented a well-advanced arteriosclerosis equal in degree to that observed in many cases of dissecting aneurysm without evidence of syphilis. Thus, in only two cases of the entire series, or 0.3 per cent, a background of uncomplicated syphilitic infection of the aorta which resulted in sufficient damage to contribute to or cause a dissecting aneurysm was found. It has been suggested that syphilis uncomplicated by arteriosclerosis does not provide the necessary pathologic background for dissection of blood between the coats of the aortic wall.

Microscopically, the pathologic changes were largely those of an atherosclerosis. In addition to the usual deposit of fat, cholesterin, calcium, and fatty acid crystals in the intima and media, evidences of inflammation in the intima and media were observed. These appeared in the form of lymphocytic nests, either isolated or perivascular, which were associated with intimal scarring by young fibrous tissue. These progressive pathologic changes preceded the aneurysmal dissection in varying degrees. The dissection itself usually started in small, localized areas of atheromatous degeneration and continued by splitting the lamina of the media by hydrostatic pressure from above. No evidence was found in any case of arteriosclerosis with occlusion of the vasa vasorum, and ischemia and degeneration of the aortic wall. There was no evidence of infarction of the aortic wall, either from embolism or

from sclerosis of the vasa vasorum, as suggested by Tyson.[15] In only one case sclerosis of the vasa vasorum was noted, and even then the changes were not sufficient to account for the areas of focal degeneration in the media. On the other hand, in several of our cases similar to those reported by Tyson, the intimal tear was not the starting point of the aneurysm and in four others the dissection was not accompanied by a tear. Furthermore, in two of our cases not included in this series, hematomas occurred in the aortic wall from rupture of the vasa vasorum in the media without extensive dissection and in the presence of an intact intima. In the one case a small organizing hematoma, about 2 cm. long, was found in the medial coat of the abdominal aorta. In the other, an organizing hematoma, about 12 cm. long, was noted in the media of the abdominal aorta. In both cases the lesions were found at autopsy and, while they were part of the process of generalized atherosclerosis, they had played no part in the clinical picture.

CASE REPORTS

The case reports of four patients with antemortem diagnosis of dissecting aneurysm of the aorta are presented.

CASE 1.—M. P., a man, aged 63 years, had dissecting aneurysm of the aorta extending from the ascending arch to the bifurcation of the abdominal aorta. The duration was fifty-four hours. There was terminal rupture into the pericardial cavity.

The patient was an Italian stevedore who did hard physical work until the onset of his terminal illness. His past history was irrelevant. He had no cardiovascular complaints.

On the morning of March 29, 1935, while at stool, he suddenly experienced weakness of the right leg which was followed almost immediately by severe substernal and interscapular pain. The paresis of the leg was transient, but the pain persisted. It was described as "tearing" in character and was extremely severe. It was most severe in the interscapular region and later extended into the lumbar region.

The patient was a well-developed and well-nourished man who was in considerable discomfort from pain at the time of examination. He had no fever. The important physical findings were limited to the cardiovascular system. The heart was slightly enlarged to the left. There was dullness in the second interspace to the right and the left of the sternum. The rhythm was regular; the pulse rate was 90 per minute. The heart sounds were forceful and of good quality. A loud to-and-fro murmur which was maximum at the aortic area was transmitted toward the apex. Peripheral signs of aortic regurgitation were present. The carotid pulsations were equal and forceful; the radial pulses were equal and Corrigan in type; and the femorals were equal. Both Traube's and Duroziez's signs were noted. Blood pressure in both arms was 190/80. The Wassermann reaction was positive.

The patient's condition remained the same for forty-eight hours, at the end of which time he experienced an exacerbation of severe substernal pain which had persisted since onset. He then began to show cyanosis of the face, neck, and upper extremities. The veins in the neck were distended. The heart sounds were diminished, and cardiac dullness increased to the right and left of the sternum. The peripheral signs of aortic regurgitation were no longer present, and the blood pressure fell to around 100/60 in both arms. The patient died about six hours after

this episode, which evidently marked the time of rupture of the aneurysm into the pericardium. He died fifty-four hours after the onset of the first symptom.

During the period of observation, which extended from shortly after the onset of symptoms until death, the patient voided only a few cubic centimeters of urine which consisted of almost pure blood. The clinical picture was typical of a dissecting aneurysm of the aorta with terminal rupture into the pericardial sac. The onset with transient neurologic signs, the character and location of the pain, the interference with renal circulation, and the presence of aortic regurgitation possibly of recent appearance indicated the diagnosis.

Autopsy.—Inasmuch as the important pathologic findings were in the heart and the aorta, the remainder of the autopsy findings are omitted.

The pericardial sac was dilated and of a peculiar purplish-blue color. It contained approximately 400 c.c. of partially fluid and partially clotted blood. The heart was slightly enlarged. A transverse tear was found in the posterior wall of the aorta approximately 6 cm. above the aortic ring. The blood had dissected from this point downward between the elastic laminae of the aorta into the pericardial cavity. Distal to the tear, blood had dissected its way between the central laminae of the aortic media for about half the circumference of the aorta on the right side. This area of dissection and splitting of the media extended down to and about the renal artery, and from this point blood had dissected upward to the right between the laminae of the renal artery. Some blood had escaped into the renal pelvis from a large infarct of the kidney. The dissection continued down to the bifurcation of the aorta where numerous thrombi were found. No re-entry of the aneurysm into the aortic lumen was present. Sections through the heart showed no pathologic changes in the endocardium, pericardium or valves, but did show a moderate sclerosis in the coronary system. No coronary thrombosis was noted. The intima of the aorta showed considerable thickening due to fibrous tissue and atherotic plaques along the entire course.

CASE 2.—R. B., a woman, aged 32 years, had dissecting aneurysm of the aorta. The duration was two years, ten months, and eight days. Onset was during pregnancy; a normal child was delivered at term by cesarean section.

The patient was first seen by her obstetrician, Dr. E. F. Anderson, on Oct. 1, 1937, when she consulted him for prenatal care. Her last menstrual period had been May 11, 1937, and her pregnancy had proceeded normally except for nausea.

Her past history was essentially negative. She had had no scarlet fever, rheumatic fever, tonsillitis, diphtheria, or pneumonia. Her cardiovascular system had been normal except for occasional "palpitation." She had been married for nine years and had had a previous normal pregnancy and labor in 1933. Except for the pregnancy (the uterus was the size of a four and one-half to five months' pregnancy) the examination was negative. No cardiac abnormalities were noted. The blood pressure in the left arm was 120/70.

On the evening of Oct. 1, 1937, while sitting in an automobile in front of her home, she experienced a sudden severe substernal pain. With assistance she was able to walk into the house. The pain was extremely severe and from the substernal area radiated upward into the neck and then downward posteriorly between the scapulae. At this point it remained and extended into the region of the xiphoid. It remained constant and severe for about thirty hours.

When the patient was first seen thirty hours after onset, she was writhing in bed with severe pain which radiated substernally from the scapular region to the xiphoid. She was a tall, well-developed young woman. She was not in shock and did not have fever. The notable findings were limited to the cardiovascular system. A sharp systolic pulsation was noted in the suprasternal notch and extended well into the left carotid artery. The heart sounds were of good quality. A rough,

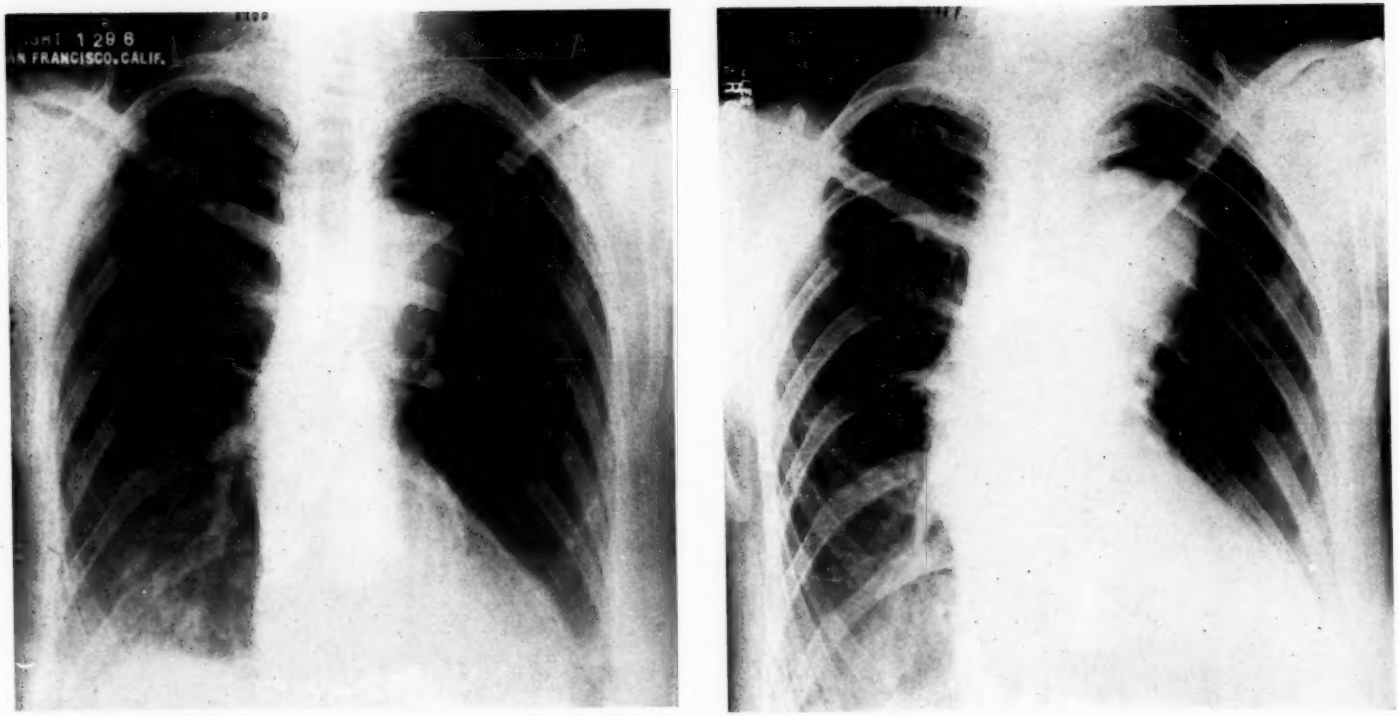
loud systolic murmur and a softer diastolic murmur were heard at the aortic area. The systolic murmur was loudly transmitted into the suprasternal notch and into the carotids. Examination of the peripheral pulses revealed the usual signs of aortic regurgitation in the left carotid, left arm, and lower extremities, and also Traube's and Duroziez's signs. The right arm and hand were cooler than the left, and the radial and brachial pulses on the right were smaller than on the left. Pulsation in the right carotid was markedly diminished, while in the left it was vigorous. Blood pressure was 130/0 in the left arm and 80/60 in the right arm; it was 160/0 in both legs.

Within a few days the pulsation in the suprasternal notch became more marked, and the aorta, which could be palpated here, was slightly tender. As time went on the pulsation in the left carotid diminished. The inequality in the radial pulses persisted; in time the right pulse became definitely retarded. Blood pressure was at all times about 120/30 on the left and 70/60 on the right. Since the dissection apparently did not progress further after the patient had been confined to bed at home for two and one-half months, she was allowed to be up and about. The first roentgen and electrocardiographic studies were made at this time (see Figs. 1 and 2).

Four months after the onset of symptoms, delivery was performed by cesarean section under spinal anesthesia (Feb. 2, 1938). The patient's postoperative course was uneventful. Until May, 1940, her condition remained about the same; although she was not completely well, she was able to be up and to attend to light household duties. During this period she had several transitory episodes of sudden weakness in the lower extremities. She also had transient periods of from five to fifteen minutes during which her visual acuity was markedly diminished. She became easily fatigued and always was conscious of palpitation. She had occasional "sticky" pains around the costal margins but never severe pain such as that which initiated the dissection. The aortic insufficiency persisted. Her heart gradually increased in size, but at no time did she show signs of congestive failure. Pulsation in the right carotid became almost imperceptible, and in the left carotid it was diminished. In February, 1940, roentgenograms showed increase in the size of both the aneurysm and the heart; also the electrocardiogram showed considerable changes (Figs. 1 and 2).

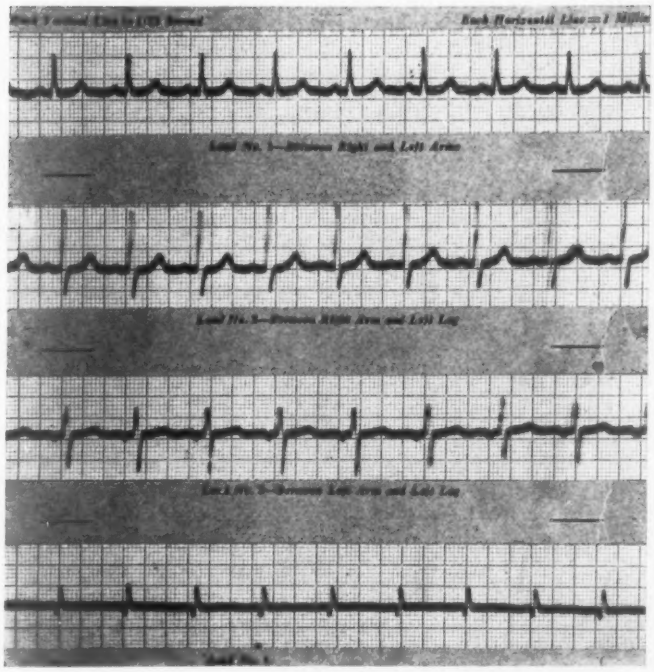
During the last three months of her life, the patient was confined to bed because of weakness and increasing bouts of pain. The pain was the same as that previously experienced and at times radiated also into the lumbar region and the right hip. Marked weakness developed in both lower extremities. No neurologic changes occurred other than hypoesthesia over the distribution of the right femoral cutaneous nerve and diminution of deep reflexes in the lower extremities. At times the patient had great difficulty in emptying her bladder; urination finally became automatic, and the bladder was continuously distended. The pulsation of the abdominal aorta gradually became less forceful, and the aorta itself seemed tender to pressure. The other peripheral vessels showed no further changes. During the last month of life, the patient became very pale and somewhat cyanotic. She had periods of faintness, breathlessness, and weakness, and attacks of "suffocation." She also had some dysphagia, especially for liquids. However, congestive heart failure did not develop, and her lungs remained clear. Her condition became slowly but progressively worse. Her death was not marked by any dramatic event such as external rupture of the aneurysm. She died on August 8, 1940, two years, ten months, and eight days after the onset of the dissection.

The laboratory findings were not important. Numerous urine examinations were normal; two blood counts were normal, and the blood Wassermann reaction was negative.

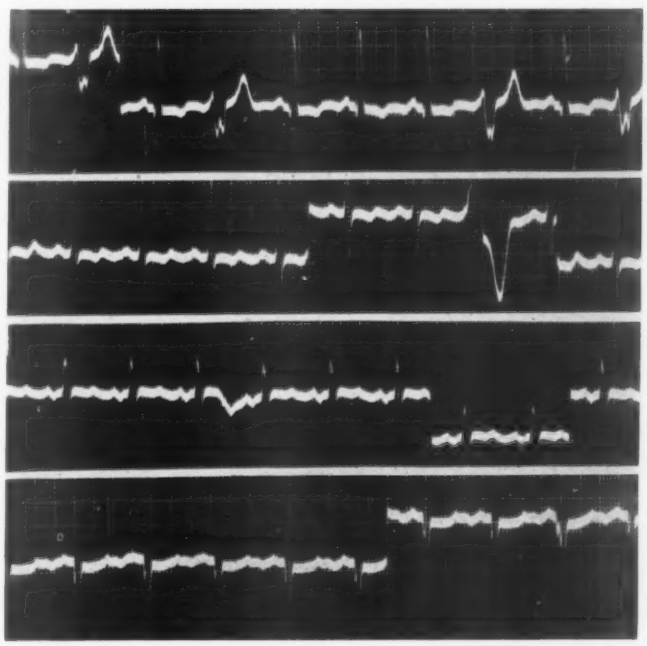


A. *B.*

Fig. 1.—Case 2. *A.* Two meter chest film two and one-half months after onset of the dissection. Note the uniform dilatation of the entire arch and upper thoracic aorta with elongation of the arch and beginning cardiac enlargement to the left. *B.* Two meter chest film twenty-seven and one-half months after onset of the dissection. There has been a marked increase in size of both aneurysm and the heart; the cardiac enlargement is on the basis of aortic regurgitation.



A.



B.

Fig. 2.—Case 2. *A*. Electrocardiogram two and one-half months after onset of the dissection. No abnormalities noted other than a left axis deviation. *B*. Electrocardiogram twenty-seven and one-half months after onset of the dissection. Changes are noted in the T waves in Leads I and II and also in the appearance of ventricular ectopic beats.

Autopsy.—No remarkable pathologic changes were found in any organs except in the heart and aorta.

The pericardial cavity contained clean visceral and parietal layers. There were only a few cubic centimeters of clear yellow fluid, but no free blood was found. The proximal 5 cm. of the aortic arch were dilated and formed a sacculation in the right and anterior aortic wall which projected forward and laterally to the right in a large, round knob about 8 cm. in diameter. This formation extended to the innominate artery and exerted considerable pressure upon it externally. In the anterior wall of the aorta, about 3.5 cm. above the aortic ring, a long, jagged, horizontal tear formed the entrance to an artificial channel which extended from this point down to the aortic bifurcation and had dissected into the left carotid artery. This channel in the aorta was crescentic on cross section; it extended through the middle of the elastic laminae of the media separating them widely, and from the front of the aorta around both sides to about 5 cm. from the midline posteriorly. In practically the same form it extended from the superior tear in the ascending aorta throughout the entire length of the aorta to the bifurcation. At that point it reentered the original aortic lumen through a horizontal tear in the anterior wall of the aorta just above the bifurcation. Thus, a second channel had been formed which extended from the ascending portion of the aorta to the bifurcation. The blood, which, in coagulating, at one time might have occluded this area, had been resorbed. The walls of the artificial channel were smooth and were lined with an adequate layer of endothelial cells. The blood had been circulating freely through this secondary channel. The original channel was patent; only its shape was changed and its caliber was reduced due to backward displacement of its anterior wall by the pressure of blood in the secondary lumen which lay anteriorly. Neither appreciable atherosclerosis nor thrombi were found in either of the channels. No lesions were found in the valves or muscle of the heart. The coronary system was patent.

Microscopic sections of the cardiac muscle showed medium-sized myofibrils separated by slight edema. The endocardium and pericardium were normal. The coronary system showed no appreciable sclerosis. In sections of the aortic wall the intima was flat and showed no thickening or infiltration with atheromatous deposits. In the media, however, the elastic laminae were deeply stained with eosin and showed an acidophilic character with some swelling of the individual elastic fibers. Between the elastic fibers and laminae a peculiar degenerative material was seen which stained blue with hematoxylin and offered an easy plane for cleavage by manual dissection. No scarring or vascularization of the media was noted. The adventitia was normal and contained numerous patent vasa vasorum which showed no sclerosis or endarteritis and carried adequate circulation into the aortic wall. In some sections large arterioles and venules extended into the media, and about several of these there were free erythrocytes.

CASE 3.*—J. K., a man, aged 54 years, had dissecting aneurysm of the aorta. The duration was twenty-nine hours. No autopsy was done.

This patient was seen for the first time at noon on Oct. 19, 1938. He had been well and working at his regular occupation of fireman until the previous day. At about eleven o'clock he had felt sudden severe mid-abdominal pain which had been followed by severe pain, tingling, and weakness in the left leg. He had not vomited. The pain had been paroxysmal in character and had not radiated into the back.

At time of examination the patient was in extreme pain. He was cold, cyanotic, and sweaty. The important findings were limited to the cardiovascular system. The heart sounds were good. Systolic murmurs were heard at the base and apex.

*By courtesy of Dr. E. L. Bruck.

The rhythm was regular, and pulse rate was 96 per minute. Pulsations in the left carotid artery were less forceful than in the right. The left radial pulse was barely palpable, but the right was normal. The right femoral pulse was normal, but the left was absent. The left leg was cold and blanched, and no pulses were elicited in the left foot.

Within one-half hour the pulsations in the left carotid, brachial, and radial arteries could not be felt. Systolic and diastolic murmurs were heard over the entire precordium. Blood pressure was 115/74 in the right arm. Severe pain continued for twenty-four hours. Gradually the pulses in the right carotid and brachial arteries became smaller, and the patient died in circulatory failure about twenty-nine hours after the onset of symptoms. Death may have been the result of a rupture into the pericardium or possibly of obstruction of both carotids. Permission to perform an autopsy could not be obtained. The onset and progress of the illness in this case were typical of a dissecting aneurysm of the aorta.

CASE 4.*—D. Mc., a man, aged 72 years, had dissecting aneurysm of the aorta. The duration was three hours. There was terminal rupture into the pericardial cavity.

This patient had been observed for a number of years. He had had rather extensive vascular changes due to arteriosclerosis, and his blood pressure usually had been about 180/100. His past history otherwise was not relevant to his terminal illness.

On May 2, 1936, while the patient was walking across his room, he had a sudden severe pain at the lower end of the sternum. The pain was felt through to the back. Later, pain developed in the right leg. When he was first seen, he was in shock, had vomited, and was cold, sweaty, and pale. The pulse rate was 100 per minute. The heart sounds were distant, and a soft systolic murmur was heard at the apex. There was severe pain in the right leg which was cold. The right femoral pulse was absent. The left femoral pulse and the left foot pulses were present. The patient's condition became progressively worse. A loud systolic and diastolic bruit developed over the upper precordium. The blood pressure could not be obtained in either arm. The patient died about three hours after onset of the dissection.

Autopsy.—The aorta showed marked atheromatous changes. The dissecting aneurysm extended along the entire vessel from the aortic ring to the bifurcation. It communicated with the lumen through a small intimal tear just above the bifurcation of the abdominal aorta. There were no other intimal tears. Death had resulted from rupture of the aneurysm externally into the pericardial cavity at the root of the aorta just inside the pericardial reflection.

COMMENT

Little has been added to the picture of dissecting aneurysm of the aorta since the report of Peacock,[4] who was the first to put our knowledge of this condition on a firm foundation with a satisfactory and well-reasoned account of the disease. He recognized that a lesion of the media formed the background for the dissection, but he considered the rupture of the intima as the initial step in the process. Shennan,[10] in his comprehensive review of 300 cases with especial attention to the pathologic aspects of the disease, also concluded that the essential change was in the media. He found that in most cases the media gave way

*By courtesy of Dr. E. L. Bruck.

before the intima and concluded that the immediate or exciting cause was a sudden increase of blood pressure due to physical or mental strains and stresses.

Our series of cases does not differ greatly from those previously reported. As has been noted, the important change is medial degeneration with weakening of the elastic laminae of the wall of the aorta. Hemorrhage from the vasa vasorum into the diseased media may occur; in some cases it is extensive and not associated with an intimal tear. For this reason Eppinger[16] (1887) called the lesion an intramural hematoma of the aorta, a term which we believe is appropriate in some instances. The base of an atheromatous ulcer is rarely the site of the intimal rupture. As a rule, the location of the tear in the intima bears no relation to disease of the intima but rather depends on underlying medial changes in the elastic lamina and on the dynamics of the aortic pulsations.

Although Shennan stressed the importance of the systolic blood pressure, he considered the diastolic recoil in the ascending aorta a more important factor in the intimal rupture. Elliotson[17] (1830) stated that the occurrence of a rupture was not necessarily dependent on an elevation in blood pressure but that it could be adequately explained on the basis of the degenerative lesion of the media. It is interesting to note that in our series the blood pressure was elevated in seven and normal in nineteen of the cases in which it was recorded. In Case 2, the blood pressure was normal a few hours before the onset of the dissection and on many subsequent occasions the systolic pressure was always the same. We believe this supports the suggestion that an elevated blood pressure is not essential for the formation of a dissecting aneurysm.

We have noted two cases in which a small dissecting aneurysm was found in the wall of the abdominal aorta. No intimal rupture occurred. The aneurysms were silent and took no part in the clinical picture. It is probably significant that in both cases the aneurysms were in the abdominal aorta. In the ascending aorta the same degree of medial change with hemorrhage and degeneration would most likely have led to an intimal tear followed by the usual course of a dissecting aneurysm. Medial change, systolic stretching, and diastolic recoil seem to be the conditioning factors for intimal rupture in the ascending aorta.

In only two of the sixty-four cases presented in this report, uncomplicated syphilitic aortitis occurred. In the nine cases in which the presence of syphilis was proved either seriologically or microscopically advanced atherosclerosis consistent in degree with that found in cases of dissecting aneurysm without syphilis was also present.

In thirty cases the patients were seen by a physician before death occurred; in the remaining thirty-four cases the patients died so suddenly that medical attendance was impossible. In seven cases diagnosis was made before death.

Case 2 was of special interest because the dissection developed during pregnancy. The relation of pregnancy to dissecting aneurysm is not yet clearly understood. In a review of the English literature, McGeachy and Paullin[18] reported twenty-four cases in females, six of whom were pregnant. This incidence is high, and it is interesting to speculate on the relationship of pregnancy to the medial changes that lead to dissecting aneurysm.

A number of recent contributions have stressed the importance of cystic necrosis of the aortic media to dissecting aneurysm of the aorta and also to spontaneous rupture of the aorta. The pathologic picture of medionecrosis aortae idiopathica cystica was first brought out by Erdheim[19] and more recently in an excellent review by Roberts.[20] The high incidence of this medial change in pregnancy is noteworthy. In Case 2 of this report the medial change was similar to that described by Erdheim although no true cystic areas were observed. In most of our series the degenerative medial change was observed in varying degree and has been considered an atheromatous type of degeneration.

The prognosis in dissecting aneurysm is generally poor. However, an extensive dissection may be repaired either by organization and fibrosis of the aneurysm and the clot in it or by endothelialization of the artificially formed tube which, following lysis and resolution of the clot, may be converted into a physiologic conductor of a fluid stream.

CONCLUSIONS

Sixty-four cases of dissecting aneurysm of the aorta are presented. This condition occurs primarily in arteriosclerosis and exceptionally in syphilis or in a combination of these. Syphilis is found in most cases of saccular aneurysm but in only a small number of the cases of dissecting aneurysm of the aorta. In this series of sixty-four cases, it was found without atherosclerosis in only two.

The point of initiation is a ruptured vas vasorum in a weakened media which forms a small spreading hematoma. The process usually occurs without demonstrable pathologic changes in the vasa vasorum but rather as a disease of the aortic media only. In rare instances the point of initiation is a tear in the intima at the site of atherotic deposits. The dissection may remain static; on the other hand, it may rupture either through the adventitia, with hemorrhage into the adjacent structures, especially the pericardial cavity, or back into the aortic lumen.

Dissecting aneurysm of the aorta is not as uncommon as hospital records indicate. Due to its rapid and fulminating character, it frequently results in sudden death so that hospitalization and medical study are precluded. Furthermore, statistics have been meager because of the incomplete or negligible records of medicolegal and coroners' offices.

External trauma is not a predisposing factor to the production of a dissecting aneurysm.

Elevation in blood pressure is not an essential factor in this condition.

The antemortem diagnosis of dissecting aneurysm of the aorta is made with increasing frequency and will be made even more often if the not uncommon occurrence of the disease is kept in mind and its characteristic findings are brought out by careful clinical observation.

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DISCUSSION

Dr. Aaron Arkin, Chicago.—I have seen a number of cases of dissecting aneurysm of the aorta and wish to make a few remarks about the pathology and clinical picture.

Most of the patients were young adults with marked hypertension. The first case which I saw some years ago in Vienna was one reported by Professor Erdheim in his fine work on the histopathology of the aorta in these cases. He described a peculiar type of medionecrosis, a non-inflammatory necrotizing process affecting the media, and producing mucoid cystlike areas of degeneration. He called this medionecrosis aortae cystica. Similar small foci have been found in the aorta in routine examinations.

One patient was a young engineer 30 years old with marked hypertension. He developed terrific substernal pain and died in a few hours. The necropsy revealed a supravalvular tear, with hemorrhage into the pericardium and heart tamponade. The aorta revealed a medionecrosis.

A few months ago I saw a young physician of 40 who had essential hypertension. While sitting in the hospital office, he developed a severe pain in the heart region which soon radiated to the back of the chest between the shoulder blades. The next day the pain was in the upper abdomen. At the onset he could neither stand nor lie down, and lay in a chair in a semirecumbent position.

The electrocardiogram was practically normal. His hypertension, profound shock, agonizing pain with radiation down the back, and normal electrocardiogram suggested a dissecting aneurysm.

The disappearance of the pulse in an arm (usually the left) or in the left carotid with the above clinical picture lends support to the diagnosis. The clinical picture may resemble an acute abdomen, perforated ulcer, or acute pancreatitis, as well as myocardial infarction. X-ray examination may be of value when a widening of the aortic arch, innominate, or left carotid shadow appears. On the other hand, there are cases of slow development with few symptoms; these patients may live for months or years.

DR. WILLIAM B. KOUNTZ, St. Louis, Mo.—I should like to say a word about hypothyroidism and this condition. When the fever of taking out thyroids for the relief of heart disease was at its height, in our clinic, four cases had thyroids removed. All of these patients were young individuals and had severe hypertension and impending cardiac failure.

The first two patients died with ruptured aortas six months after the operation. Because of this, the other two were put on thyroid. One, the third case, lived for two and a half years, and finally, on her own initiative discontinued thyroid treat-treatment; she died six or eight months later, with a ruptured aortic aneurysm. The fourth patient is still living under pressure of thyroid therapy.

Our pathologist, Dr. Robert Moore, diagnosed the slides as being, as Dr. Arkin has suggested, Urdheim's disease or a cystic necrosis of the aortic muscle.

I should like to ask the essayist if any of these cases, especially the cases he had a chance to follow, showed any hypothyroidism clinically.

It is possible to demonstrate muscle degeneration in animals by taking out the thyroid. I had never seen ruptured aorta in animals, but aortic degeneration occurs. Dr. David Barr has reported a case of clinical myxedema since our experience with induced hypothyroidism in May with a basal metabolism of minus 36. In his case there was degeneration of the aortic muscle and also of the smooth muscle of the intestinal tract.

DR. EUGENE S. KILGORE, San Francisco.—Dr. Mote and Dr. Carr have done well to introduce the subject of dissecting aneurysm, which, as they show, is less rare than is commonly supposed. The condition has only recently begun to be diagnosed clinically, and certain details of the clinical picture still need clarification. Two such details are especially worthy of attention by those who report cases.

One is the question of strain as a precipitating cause, which will certainly require medicolegal consideration. Among the cases thus far reported, physical activity has immediately preceded the pain with sufficient frequency to be probably significant. But the exertion has often been mild and may be overlooked without careful questioning. In several reported cases it was straining at stool; in a pregnant woman it was the act of stooping; in a patient of mine it was the act of reaching high up to insert an electric bulb; and in another it was leaning over a table. Middleton reported the case of a man in whom pain began suddenly while

he was removing an overcoat. Shennan described one whose attack began while he was swinging onto a bus, and another who was tolling a bell. All are instances of mild exercise, but suggest contortion of the thorax as a precipitating cause of dissection. Other histories, like that of Dr. Mote's patient, clearly exclude such a factor, but the bulk of the published case reports leave the question of strain unanswered.

The other detail needing more exact description is the character of the pain as distinguished from its location, especially the presence or absence of throbbing. This was denied by two patients recently seen and was described by another of mine and by a patient of one of my colleagues. But the information was obtained only by direct questioning, and it seems not improbable that throbbing has often been present when not mentioned in case reports. For it is easy to understand a rhythmic aggravation of pain when successive pulse waves are splitting the aorta bit by bit or stretching the newly formed aneurysmal cavity, and it is possible that throbbing pain will be found to be a significant symptom of advancing aortic dissection.

DR. MAURICE S. JACOBS, Philadelphia.—A week ago yesterday, I had the sad duty to go to the funeral of my cardiac chief in Philadelphia, who died of a ruptured dissecting aneurysm. We had known for about two years that he had dissecting aneurysm following hypertension of many years' duration. He had been invalided because of progressive cardiac anoxemia, with minor episodes that from time to time suggested acute myocardial infarction.

The interesting thing was the unusual site of that rupture, which was posteriorly, and into the esophagus, resulting in massive hemorrhage. As fast as he could get blood by transfusion he lost it. He finally died five days after the sudden rupture which occurred while he was absolutely quiet in bed.

DR. CLOUGH T. BURNETT, Denver Colorado.—Those discussing the paper have not mentioned the recurring type of pain which occurs in these people who do not die in the initial attack.

A restaurant man in the late fifties, who had been known to be moderately hypertensive, attempted to carry a light coffee urn. He had a terrific pain, was in shock, and was considered to be in an attack of coronary thrombosis.

He was in such extreme shock that the initial examination was limited mainly to the heart. His pain disappeared for probably six or eight hours, but recurred over a period of about five days. Each time the pain was a little more severe. With repeated bouts of pain, there was at no time any E.K.C. evidence of coronary occlusion. About the third day, when I saw him in consultation, it was noted that he had a dullness in the left chest, without associated symptoms or signs that would indicate pneumonia. He did not have temperature elevation, but some leucocyte increase. X-ray examination suggested left upper lobe pneumonia.

In an attempt to determine what this dullness might represent, a needle was introduced and pure blood was obtained. He died about five days after the onset. Autopsy showed a dissecting aneurysm probably 8 cm. in length, finally perforating into the left pleura, with an enormous amount of blood in the left upper pleura.

DR. DREW LUTEN, St. Louis.—Although at present dissecting aneurysm of the aorta is regarded as almost invariably fatal, and it is indeed almost impossible to make an unequivocal diagnosis without autopsy, yet in view of the fact that here and there cases are observed in which the patient later is shown to have survived, the question must arise whether future years will not witness a considerable increase in the number of patients who do not succumb.

While one could hardly expect the mortality in dissecting aneurysm to be other than very high, yet subsequent years may in some degree duplicate the history of coronary thrombosis in which earlier conceptions of the mortality have had steadily to be revised downwardly.

In the case with restricted blood flow in the renal artery I am not sure whether Dr. Mote stated the blood pressure. I should like to ask him what the blood pressure was in that case.

DR. HERMAN E. PEARSE, Rochester, N. Y.—This discussion has pertained to dissecting aneurysm in a diseased arterial wall. I merely wish to say that it is possible with traumatic rupture of the aorta to anticipate a different course of events and perhaps a better prognosis. The basis for this statement is from the observation in aortic surgery that it is almost impossible to keep a small wound of the aorta open long enough to have extravasation of any magnitude. It is impossible to produce dissecting aneurysm in a dog because of the rapid healing of the vessel.

In patients whom I have seen with apparent dissecting aneurysm due to traumatic rupture of the aorta there has been no sign or symptom of difficulty from the lesion. One individual lived a week and then died of pneumonia in a traumatized lung; at post-mortem examination his aortic lesion was rapidly healing. Thus in the healthy, undiseased aortic wall, one may anticipate a picture simulating dissecting aneurysm but having a different course.

DR. T. J. DRY, Rochester, Minn.—I wish to add to the discussion one symptom or group of symptoms to which no reference has been made thus far, namely, those symptoms referable to the central nervous system. These consist of transitory weakness and paresthesia noted in the upper extremities. These are due to temporary interference with the blood supply to the spinal cord. It will be remembered that the spinal cord receives part of its blood supply from the intercostal vessels and during the dissection of the aorta these may be interrupted. At a later date the same evidence may occur at lower levels with symptoms corresponding to the spinal segments involved. This group of symptoms may be very helpful in the diagnosis of some of these cases.

DR. CLAYTON D. MOTE, San Francisco, Calif.—I am, indeed, grateful for the discussion. Many points are brought out that have been impossible for me to mention this afternoon and time will not allow detailed discussion now.

Dr. Yater brings up a practical point in differential diagnosis. I believe the location of the initial pain is very important in the differentiation of saddle embolus and dissecting aneurysm of the abdominal aorta. The pain of saddle embolus is in the legs, because of ischemia. The initial pain in a dissecting aneurysm arises in the wall of the aorta and appears in the back, abdomen, or thorax. As the dissection progresses and occlusion of an iliac artery subsequently occurs, pain appears in the legs and is indistinguishable from that of a saddle embolus.

We have not noted the association of myxedema and dissecting aneurysm as mentioned by Dr. Kountz. One wonders about a possible relation to cholesterol metabolism.

THE INCIDENCE OF HEART DISEASE IN MEXICO

A Study of 2,400 Cases of Organic Heart Disease

Ignacio Chávez,* M.D.
Mexico City, Mexico

SEVERAL statistical studies on heart disease have been published recently. Those from the United States, England, Czechoslovakia, and Argentina are particularly extensive and interesting. They inquire into the real importance of the different causes of organic disease of the heart and are intended to help the physician make an etiologic diagnosis in each case and to learn something about the prevention of heart disease. In order to appreciate the importance of the many possible causes, it would be very helpful if all countries would contribute their own statistics. The significance of factors such as race, climate, kind of work, and living standards, in increasing or decreasing the effect of universal causes, would thus be made apparent.

Mexico has not yet produced such a report, and this paper attempts to fill the gap by presenting the results of my personal experience. As will be seen, many of my data are similar to those from other countries, but some are entirely different, particularly with respect to diseases which affect the Indian race.

MATERIAL

I have taken 726 cases from the cardiological service of the General Hospital. These patients were admitted during the last ten years. They were examined clinically, roentgenologically, and electrocardiographically, and laboratory studies were made in an attempt to ascertain the etiology in each case. To these I have added 1,674 private patients who were examined in the last five years; practically all of them were subjected to the same kind of study. Occasionally, in cases in which the diagnosis seemed obvious, no laboratory data were obtained. All of the 2,400 patients had demonstrable organic heart disease, except those with hypertension and thyrotoxicosis, who, for obvious reasons, were included. Patients with "functional" or neurotic cardiac complaints, who, as is well known, never develop heart lesions, were intentionally excluded.

In evaluating the results, it is important to note that the hospital patients were from a charity ward, and belonged to a very low income group; they were of mixed Indian and white blood (mostly Indian), or pure Indian. Some were farmers and others were city laborers; all lived under poor hygienic conditions. The private patients, on the other hand, were a heterogeneous group of pure whites and mixed

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*Professor of Medicine, University of Mexico. Physician in Charge of the Cardiological Service, General Hospital.

races of all kinds. Some were intellectuals, and others were manual laborers from the city and country. Their economic status and living conditions were better than those of the other group.

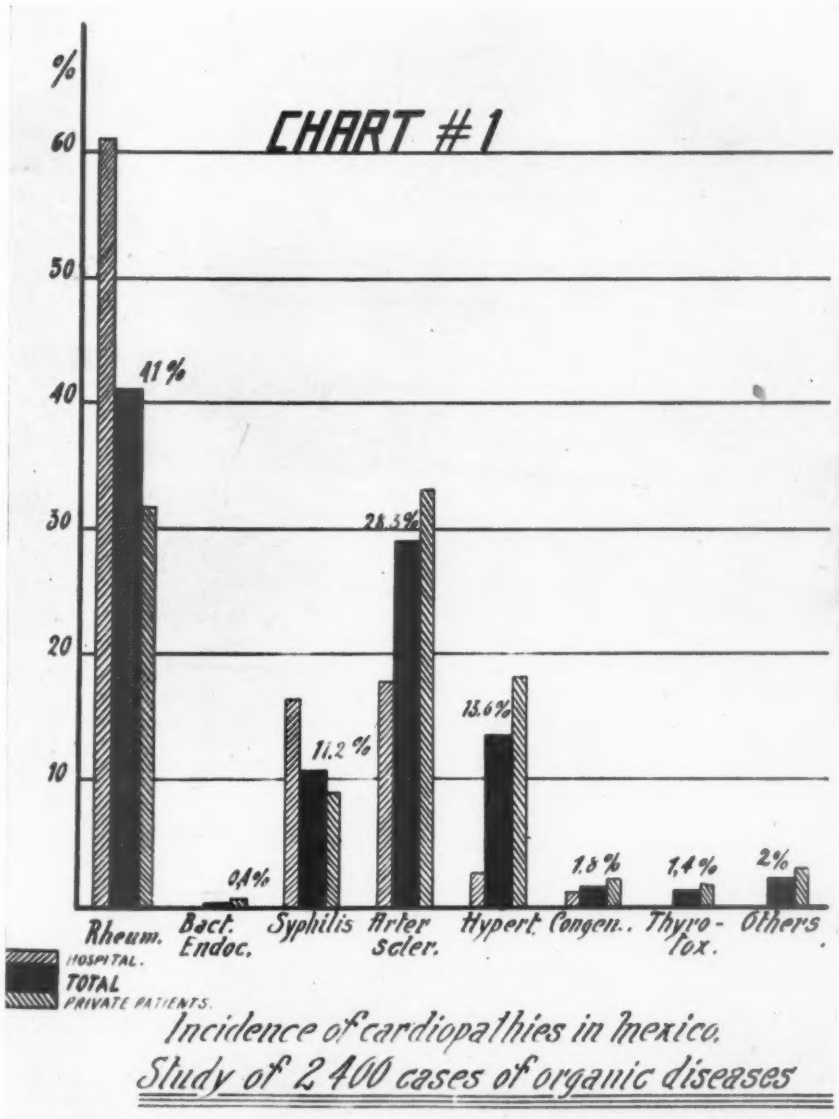
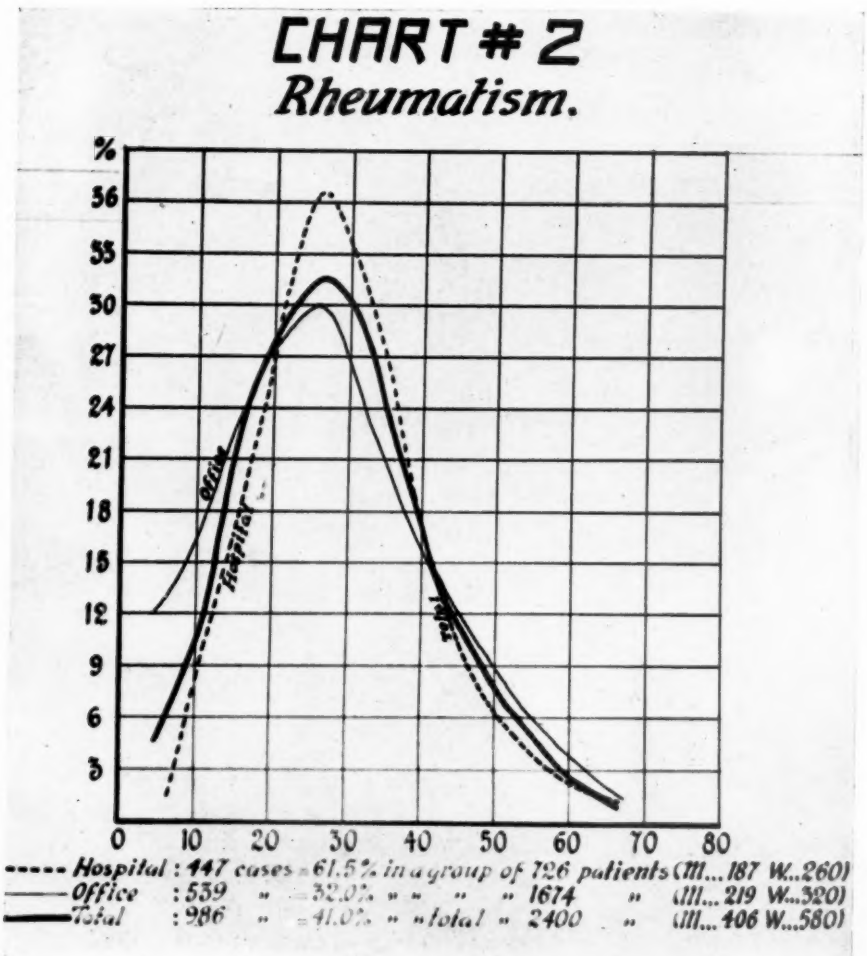


Table I and Chart 1 summarize the incidence of the various kinds of heart disease. The distribution in the two groups is somewhat different, particularly with respect to rheumatic heart disease and hypertension. It will be seen that the former was twice as common among the hospital patients, whereas the incidence of the latter was *seven times greater* among the private patients. This deserves further discussion.

TABLE I

	PRIVATE PATIENTS	PER CENT	HOSPITAL PATIENTS	PER CENT	TOTAL	PER CENT
Rheumatic heart disease	539	32.1	447	61.5	986	41.0
Bacterial endocarditis	9	0.5	–	–	9	0.4
Syphilis	147	8.8	123	16.9	270	11.2
Arteriosclerosis	551	32.9	128	17.6	679	28.3
Hypertension	309	18.4	19	2.6	328	13.6
Congenital heart disease	34	2.0	9	1.2	43	1.8
Thyrotoxicosis	35	2.0	–	–	35	1.4
Miscellaneous (cor pulmonale, anemia, cause not ascertained)	50	3.0	–	–	50	2.0
	1,674	99.7	726	99.8	2,400	99.7

Private patients	1,674
Hospital patients	726
Total	2,400



RHEUMATIC HEART DISEASE

The incidence of rheumatic heart disease in the 2,400 cases was 41 per cent, which is about the same as that reported by White and Jones,[1] in Boston (39.5 per cent), Wyckoff and Lingg,[2] in New York (42.7 per cent), Coombs,[3] in England, and Brumlik,[4] in Prague (40.5 per cent), but is lower than that reported by Ormhaug, in Norway (50.8 per cent). However, it is significantly higher than that encountered by Cossio,[5] in Argentina (17.9 per cent, leaving out "functional" heart disease), and nearly four times as high as that reported from Texas by Schwab and Schulze[6] and Stone and Vanzant[7] (10 per cent in the white race and 3.6 per cent in Negroes). This incidence of 41 per cent, which is approximately as high as the highest in the world, destroys the myth that rheumatism is a rare disease in tropical or semitropical countries.

The incidence of rheumatic heart disease among the hospital patients was enormous (61.5 per cent); I know of no higher figure. It indicates not only a relative, but also an absolute, increase in the prevalence of the disease. The relative increase resulted from the scarcity of hypertension in the hospital group. When the latter is excluded, all of the others increase, but, even so, the incidence of rheumatic heart disease is disproportionate. The reason is not clear, but one wonders whether racial predisposition, poor hygiene, and the prevalence of chronic tonsillar infections among hospital patients may be factors.

The sex incidence among the hospital patients (males, 187; females, 260) and private patients (males, 219; females, 320) was exactly the same (males, 41 per cent; females, 59 per cent). Chart 2 shows that the peak of incidence occurred in the third decade.

CARDIO-AORTIC SYPHILIS

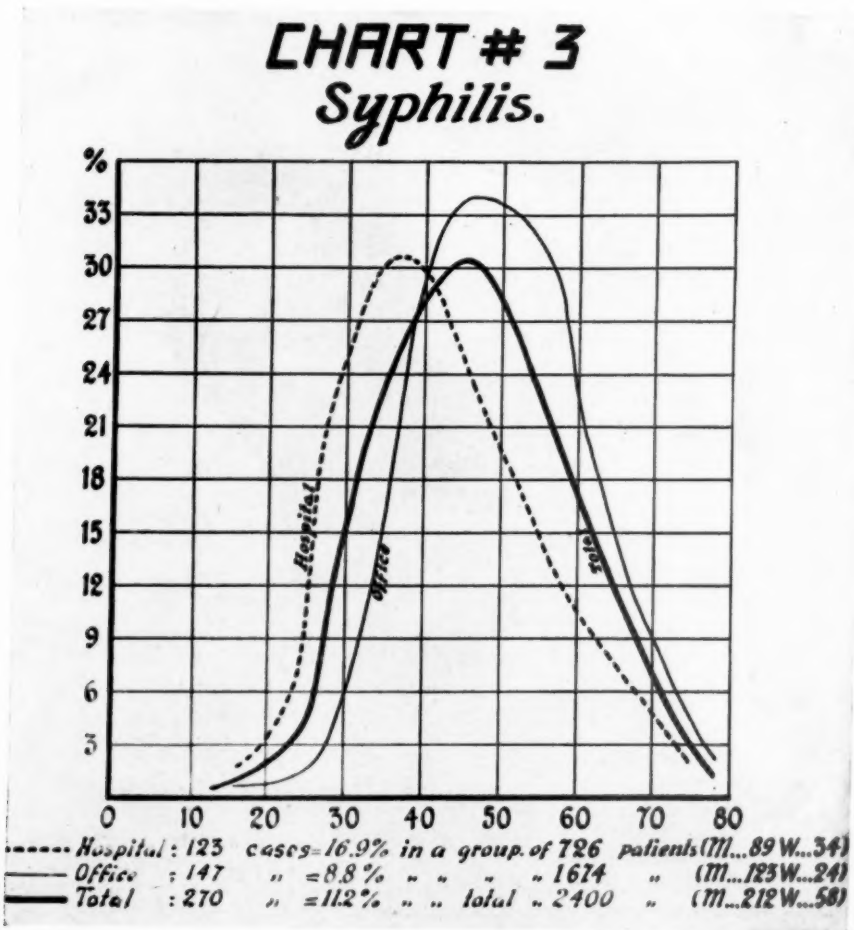
Chart 3 shows that the incidence of syphilis was about twice as high among the hospital patients (16.9 per cent) as among the private patients (8.8 per cent). The mean incidence (11.2 per cent) is higher than that in the northern part of the United States (2 to 7 per cent), Czechoslovakia (4.1 per cent), Argentina (6 per cent), and England (6.5 per cent), and lower than that in the southern part of the United States, where it is 15 to 31 per cent among Negroes. In Mexico, as elsewhere, males predominate in a proportion of about 3 to 1. The peak of incidence occurred in the fourth and fifth decades.

Of these 270 patients, 60 per cent had aortitis and valvular lesions, 6.2 per cent had aortic aneurysms, and only 72 per cent gave positive serologic reactions. These figures are similar to those which emerged from my analysis,[8] several years ago, of 132 cases of syphilitic aortitis.

HYPERTENSION

Chart 4 shows the incidence of pure hypertension, unaccompanied by demonstrable arteriosclerosis or angina pectoris. The striking difference,

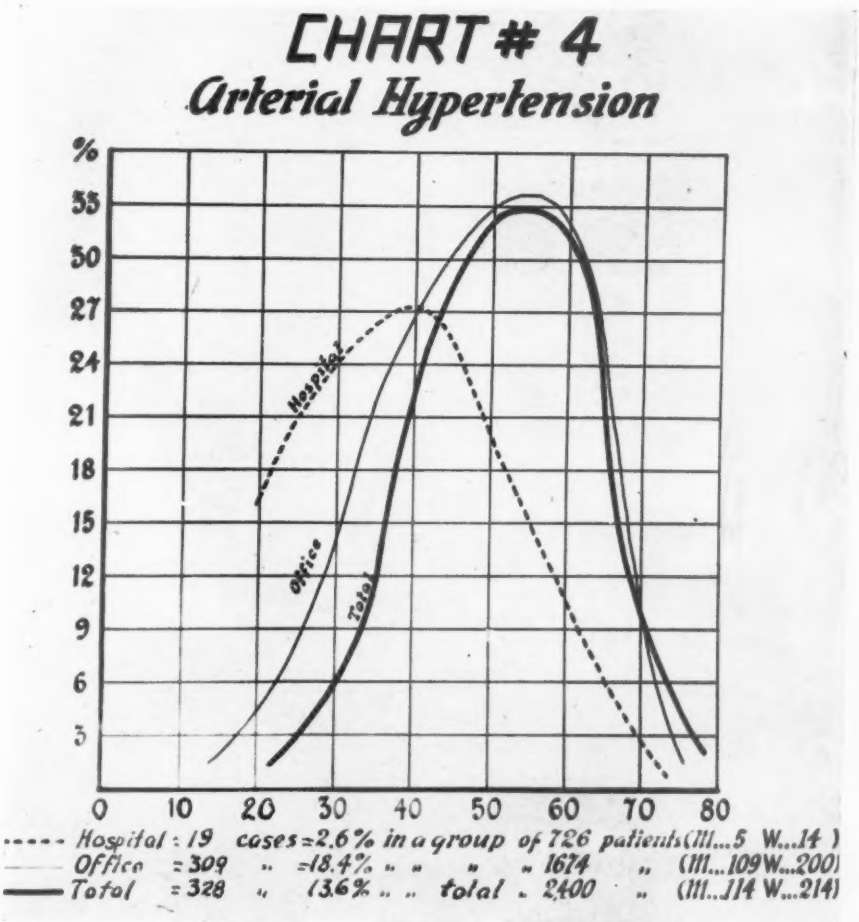
previously mentioned, between the private patients and hospital patients (18.4 per cent and 2.6 per cent, respectively) does not tell the whole story. It is well known that patients with hypertension who have no symptoms of coronary disease or of arteriosclerosis in other organs are not likely to be hospitalized. Furthermore, we meet with the difficulty in classification which was so well pointed out by White and Jones,[1] namely, that the patients with hypertension and arteriosclerosis have to be included with the pure hypertensives. Therefore, to the 328



cases of pure hypertension we must add 343 of the "hybrid" group, which makes a total of 671 cases of hypertension, or 27.9 per cent of the total. However, when this is done in the hospital group, we still have only 7.3 per cent, which is one-fifth of the incidence among the private patients. Such a disproportion does not exist among other etiologic factors, nor in other countries or races. On the contrary, among the Negroes of Texas, Stone and Vanzant[7] and Schwab and Schulze[6] found

that the incidence of hypertension ranged from 50 to 57 per cent, and that malignant hypertension was unusually common.

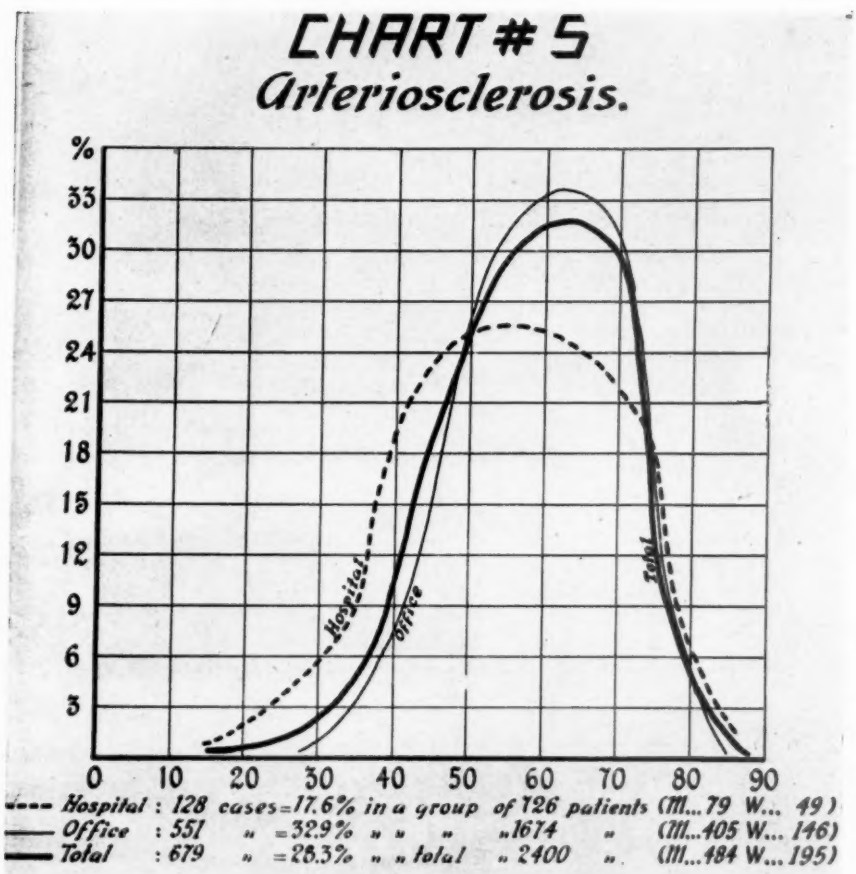
Among our Indians the situation is just the opposite. I have said that our hospital population is made up of mixed-blood "mestizos" (who are mostly Indian) and pure Indians. Their food and hygienic conditions are poor, but in this instance these factors do not seem to play a role. I am inclined to think that there is a racial factor which operates through a nervous mechanism. For centuries the Mexican



Indian has lived a slow and unharassed life. His manual labor may sometimes be strenuous, but he knows nothing of uneasiness or anxiety. His philosophy of life is conformist, if not fatalistic. He has a well-balanced nervous system which protects him from the ordinary impacts of life, and he knows nothing of psychasthenia. What we call civilized living either does not reach him, or, if it does, fails to traumatize his mind. This may explain his relative freedom from hypertension, angina

pectoris, and coronary occlusion. Those who think that a nervous mechanism is an important, if not the sole, factor in the pathogenesis of these diseases may possibly find support for their point of view in this peculiarity of the Mexican Indian.

It would be interesting to know whether the Indians of Central and South America—and perhaps those of the United States—enjoy the same immunity, and to follow the Mexican laborer who stays in the United States for a long time, to see how he fares with respect to hypertension, angina pectoris, and myocardial infarction.

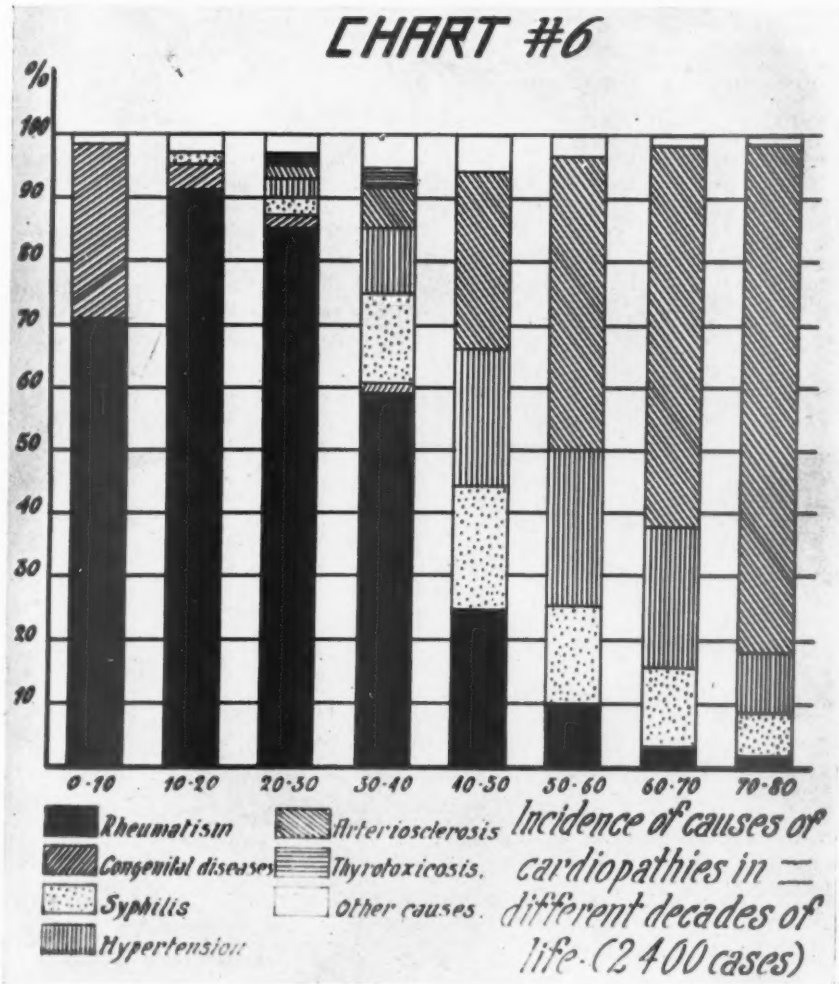


ARTERIOSCLEROSIS

Chart 5 shows the incidence of arteriosclerosis, with and without hypertension. The mean is similar to that in other countries. It should be noted that the incidence among the private patients was almost twice that in the hospital group. The males predominate, 3 or 4 to 1. Fifty per cent of the arteriosclerotic patients also had hypertension, and the proportion was higher among the private patients (56 per cent) than in

the hospital group (26.5 per cent). The incidence of arteriosclerosis among our Indians is not much lower than in other countries, and that is why the extreme infrequency of hypertension, angina pectoris, and coronary thrombosis is so striking.

Chart 6 summarizes the incidence of the various kinds of heart disease in the different decades of life. In the first two decades, rheumatic and congenital heart disease predominates, whereas, after the age of 60, arteriosclerosis and hypertension preponderate.



SUMMARY AND CONCLUSIONS

1. A series of 2,400 cases of heart disease was analyzed. Seven hundred twenty-six of the patients were taken from the cardiological service of the General Hospital, and were seen during the last ten years. The remainder, numbering 1,674, were private patients whom I examined in

the last five years. Leaving out disturbances of nervous origin, Table II gives the incidence of the various kinds of heart disease.

TABLE II

	NO. OF CASES	PER CENT
Rheumatic heart disease	986	41.0
Bacterial endocarditis	9	0.4
Cardio-aortic syphilis	270	11.2
Hypertension	328	13.6
Arteriosclerosis	679	28.3
Congenital heart disease	43	1.8
Thyrotoxicosis	35	1.4
Miscellaneous (cor pulmonale, anemia, cause not ascertained)	50	2.0
Total	2,400	99.7

2. The fact is emphasized that in Mexico, with its diversified, but predominantly semitropical, climate, rheumatic heart disease is as prevalent as it is in England and the northern part of the United States. Attention is also called to the enormous incidence (61.9 per cent) of rheumatic heart disease in the poor and the Indian population (either pure or with a little admixture). This figure is probably not exceeded in any other country.

3. Pure hypertension is very rare among the poor and Indian population. The incidence was 2.6 per cent, and rose to only 7.3 per cent when the arteriosclerotic cases with hypertension were added, whereas, among the private patients, who were pure white, or "mestizos" with a little Indian blood, the incidence was 36.9 per cent. It is suggested that the slow and unharassed life which the Mexican Indian has lived for centuries explains this disproportion.

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DISCUSSION

DR. GEORGE HERRMANN, Galveston, Texas.—We are certainly most deeply indebted to Professor Chávez for making the long trip to bring to us these striking original statistics. Those of us who have visited Dr. Chávez in Mexico have enjoyed his gracious hospitality and have been impressed by his demonstrations and observations.

I have made many holiday trips to Mexico to learn the "mañana attitude" as a preventative for hypertensive disease, and also to learn from Professor Chávez the story of rheumatic carditis in Mexico. This prompted our comparative study, recently interrupted by illness but partially presented at Boston, of the matter of rheumatic carditis in various localities in the South.

From autopsy studies we learned of the relatively high incidence of rheumatic carditis at Atlanta (3 per cent, Claybourne and Wolfe). In New Orleans, between 1920 and 1930, the figures were about the same, about 3 per cent, but in the last decade the autopsy incidence has dropped to about 1.5 per cent, according to Baker and Houlebek. In Galveston, the percentage was found to be 0.8 per cent. Traveling further west, to the El Paso area, and the plateau in west Texas, which is an extension northward of the Mexican plateau, we find a definite increase again in rheumatic carditis. This reaches through the Texas panhandle into the Rocky Mountain region, where there is much rheumatic carditis which Dr. Burnett could tell us more about. The altitude, I believe, must be a factor in that.

We have noted in our series that about 50 per cent of the patients have come from outside Galveston, Texas, and the Southwest, and second, that the average age at death of our rheumatic cardiacs is considerably higher than elsewhere.

Is the rheumatic patient, after he comes to the Southwest, doing better? Apparently he lives longer. Is there not a possibility that the disease often heals completely in the Southwest?

I do not think that we can emphasize too much the significance of the studies that Dr. Chávez is making. His Institute of Cardiology is certainly the broadest in its scope in the hemisphere, and probably in the world. It is an ideal concept which we should emulate. It will probably continue to furnish us with important data on the etiology, epidemiology, social side, and many other phases of cardiovascular disease.

DR. T. DUCKETT JONES, Boston.—With Dr. Herrmann, I would like to add my congratulations and thanks to Dr. Chávez for coming so far to give us this interesting information. The data seem more pertinent to rheumatic fever and rheumatic heart disease than to any other phase of cardiovascular disease.

It is a paradox, as pointed out by Dr. Herrmann, that, as one proceeds south of an area where the incidence of rheumatic heart disease is low, one finds this very high incidence reported by Dr. Chávez. Many little understood, possible explanatory features come to mind, such as climate in general, latitude, altitude, and the influence of the clinical patterns of hemolytic streptococcus infection. Regardless of what ideas one has concerning the etiology of rheumatic fever, there seems but little doubt that, from a public health point of view, rheumatic fever follows very closely the epidemiology of hemolytic streptococcus infections.

We are rapidly having to change our ideas concerning the epidemiology of rheumatic fever. For instance, Dr. Paul has reported the highest known incidence of rheumatic heart disease among the Indian school children of Montana and Wyoming. Previous ideas that there was a high incidence only in damp areas or at low altitude are hence untenable. This report helps stress the need of more extensive and comparable epidemiological studies.

I should like to ask Dr. Chávez what the general picture of hemolytic streptococcus infection is in Mexico City. Are there many cases of scarlet fever, otitis media, tonsillitis, and pharyngitis? These considerations seem very vital to the problem.

Dr. Chávez's report of this high incidence of rheumatic heart disease in Mexico City indicates that there must be an even higher incidence of rheumatic fever.

PROFESSOR IGNACIO CHÁVEZ, Mexico City, Mexico.—I said in my paper that I reserve for another study an analysis of the data on rheumatic heart disease, hypertension, and so forth. I presented here only the statistics. That is the reason I did not treat some of the points touched on by Dr. Herrmann and Dr. Jones.

It is true that, as Dr. Herrmann says, there is a good reason for the high incidence of rheumatic heart disease in Mexico City. The altitude is very high, about 7,000 feet. The climate is not tropical. We enjoy a very pleasant winter and summer. In fact, we can say that there is no winter or summer.

In the General Hospital at Mexico City there are people from all parts of the country, not only from Mexico City. Here in Cleveland you have a preponderance of patients from Ohio, and, in Boston, I think you have patients from the New England states. But in Mexico City it is different. There we have patients from all parts of the country. Of course they are more numerous from the states that are near Mexico City, but it is a coincidence that these states are almost all in the high plateau. It is the same altitude and the same kind of climate, and that is the great cause, I think, of this tremendous incidence of rheumatic heart disease.

Also, among our poor classes the incidence of infections of the throat is very, very high. We were astonished when we studied the frequency of chronic tonsillitis at autopsy. Professor Costero, one of the pathologists from Spain who is working with us in the cardiologic studies, told me that he was surprised to see the enormous number of chronic infections of the throat in the hospital patients, as compared with the incidence in Europe.

Perhaps that is a real factor in this tremendous incidence. Between 80 and 90 per cent have chronic infections of the tonsils at autopsy.

There is a third reason. As I have said, the Indians do not have hypertension, and there is not a high incidence of arteriosclerosis among them. All the rest in the statistics is for rheumatic heart disease and syphilis.

I shall try to give more details in an analytical study of each of these four larger groups later.

THE SIZE OF THE HEART AS A GUIDE TO THE TREATMENT OF ADDISON'S DISEASE WITH DESOXYCORTICOSTERONE ACETATE

THOMAS H. MCGAVACK, M.D.
NEW YORK, N. Y.

AN INCREASE in the size of the small heart characteristic of untreated Addison's disease has been observed following adequate hormonal therapy.[1] This change is reflected in teleroentgenograms which show a rising cardiothoracic ratio (C. T. R.), an enlarging frontal cardiac area (F. C. A.), and an expanding heart volume per square meter of body surface (H. V./M² B. S.). In the absence of satisfactory criteria for determining the maximum safe therapeutic dose of desoxycorticosterone acetate, cardiac size has been studied in relation to the condition of the patient while under treatment with the drug. As a result of these studies, it seems possible to formulate a definite plan of management in which the changing size of the heart acts as an indicator for the amount of sodium and desoxycorticosterone acetate to be employed in the individual patient at any given time.

METHODS AND RESULTS

The study is based upon the observation of eleven patients with Addison's disease, of whom seven have been treated with desoxycorticosterone acetate* for periods varying from ten weeks to two and one-half years.

The cardiothoracic ratio, frontal cardiac area, cardiac volume, surface area, serum sodium, and serum potassium were estimated by methods previously described.[1] Comeau and White[2, 3] have called attention to the many potential factors of error present in any mensuration of the heart in vivo. Time of day, position, and relationship of food ingestion are important. In serial teleroentgenography of the heart, several points cannot be overemphasized: (1) Tube distance must be accurately measured. (2) The tube must be accurately and consistently centered over the same spot whenever examinations are repeated. (3) The same phase of respiration must be used in the taking of all pictures (the very end of a deep inspiration). The last factor is the one most often not fully

From the Department of Medicine, New York Medical College, and Medical Services of Flower and Fifth Avenue Hospitals, and Metropolitan Hospital, New York City.

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*Desoxycorticosterone acetate in oily suspension for injection and sterile compressed tablets for subcutaneous implantation were furnished by Dr. Max Gilbert, of the Schering Corporation, whose courtesy is herewith gratefully acknowledged.

controlled. Measurements are useless unless it is carefully checked. The difference between expiration and inspiration is made obvious by a single example (Table I).

TABLE I

STAGE OF RESPIRATION	CARDIOTHORACIC RATIO	FRONTAL CARDIAC AREA (SQ. CM.)	HEART VOLUME PER M^2 BODY SURFACE (C.C.)
Inspiration	0.46	131.8	546
Expiration	0.35	102.3	426

In order that we may be sure two films are comparable, one may be superimposed upon the other; or the number of ribs above the diaphragm shadow may be counted; or the distance from the first rib to the shadow of the diaphragm in the midclavicular line may be measured. Variations up to 1 cm. in this last measurement may be disregarded. Moreover, the changes in the size of the heart are so striking that at times larger errors of method can be ignored.

Of 107 observations of cardiac size, eleven were made during crisis or impending crisis; eighteen, during cortical insufficiency without crisis; seventy-five, during periods of stabilization under adequate therapy; and three, when signs of toxicity from overdosage with desoxycorticosterone acetate were present. The usually accepted clinical criteria for the fully stabilized patient are a sense of well-being with return of a greater part of former vigor, a *slow, steady* gain in weight, a return of appetite, and a rising or well-sustained blood pressure. Crisis or impending crisis has been recognized only in those patients in whom salt and water balance has been disturbed sufficiently to effect a reduction in blood volume.

TABLE II

RANGE OF VALUES OF CARDIAC MEASUREMENTS IN PATIENTS WITH ADDISON'S DISEASE (107 OBSERVATIONS)

STATUS OF PATIENT	NO. OF OBSERVATIONS	C.T.R.		F.C.A. (SQ. CM.)		HEART VOL./M^2 BODY SURFACE (C.C.)	
		RANGE	AV.	RANGE	AV.	RANGE	AV.
Crisis or impending crisis	11	0.25-0.36*	0.328	57.6- 92.0*	76.8	208.1-383.7	302.4
Insufficiency	18	0.32-0.45	0.370	79.0-100.0	88.5	277.4-466.4	367.9
Full stabilization	75	0.40-0.51	0.435	95.0-143.0	117.1	337.8-603.6	455.8
Overtreatment	3	0.51-0.58	0.546	141.0-143.0	141.7	625.1-693.0	664.5

*Except flat chests. One patient in impending crisis showed a C. T. R. of 0.42, but the horizontal depth diameter was only 7.0 cm. so that the heart volume (228 c.c.) was actually much reduced.

Results are summarized in Table II. While there is considerable overlapping of values from one adrenocortical state to the other in such a composite chart, the average figures are sharply separated. Moreover,

if the course of a single patient is followed by serial examinations, there is no confusion of values whatsoever (K. K., Table III):

TABLE III

CARDIAC MENSURATION IN VARIOUS PHASES OF ADDISON'S DISEASE (CASE K. K.)

C.T.R.	F.C.A.	HEART VOL./M² B.S.
Crisis or Impending Crisis		
0.25	57.6	208.1
0.26	74.2	263.6
Insufficiency		
0.32	83.8	296.2
0.38	79.6	277.4
0.34	92.4	322.0
Stabilization		
0.42	110.6	371.9
0.39	101.8	337.8
0.41	113.0	379.7
0.42	119.0	385.3
0.40	113.8	439.0
0.50	134.8	528.0
0.43	143.4	550.0

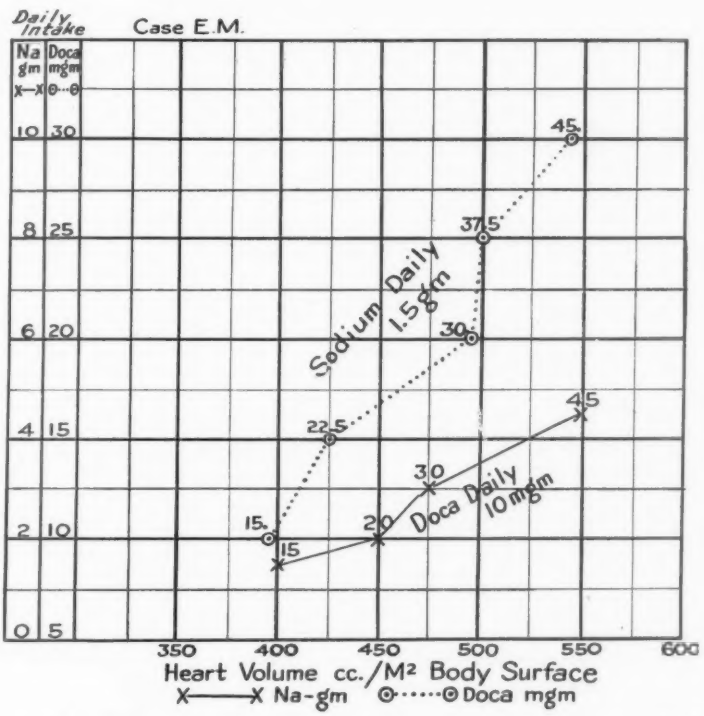

Fig. 1.—Influence of the product Na × D upon cardiac volume. (Numerals beside each calculation denote the product used for ten days or more prior to the observation.)

Two factors primarily involved in increasing the size of the heart in the patient with Addison's disease under adequate treatment with desoxycorticosterone acetate are the amount of drug itself and the amount of sodium ingested. If the daily intake of sodium is kept constant, then the size of the heart will vary directly as the amount of

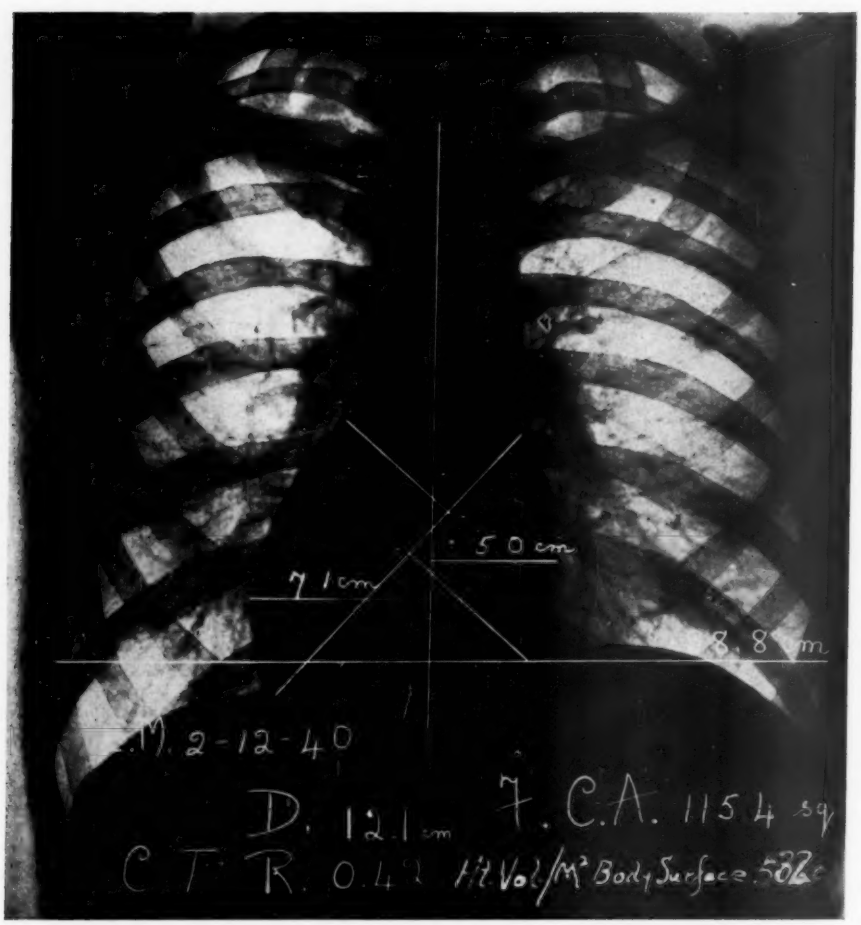

Fig. 2*A*.—Case E. M. The teleroentgenograms (Fig. 2*A* and *B*) illustrate the fact that either the intake of sodium or desoxycorticosterone acetate may be varied without appreciably changing the size of the heart just so long as the product of the two remains constant, according to the formula Na. × D = K. *A*. Na = 6 Gm.; D = 7.5 mg.; and K = 45.

desoxycorticosterone administered (Fig. 1). Conversely, if the same amount of hormone is supplied from day to day, the cardiac measurements will vary directly as the amount of sodium given (Fig. 1). The technical difficulties encountered in accurately measuring the heart have thus far made it impossible to express the above facts mathematically,

but it would appear that a straight line relationship probably exists in so far as multiple estimations in each of a series of patients are concerned (Fig. 1).

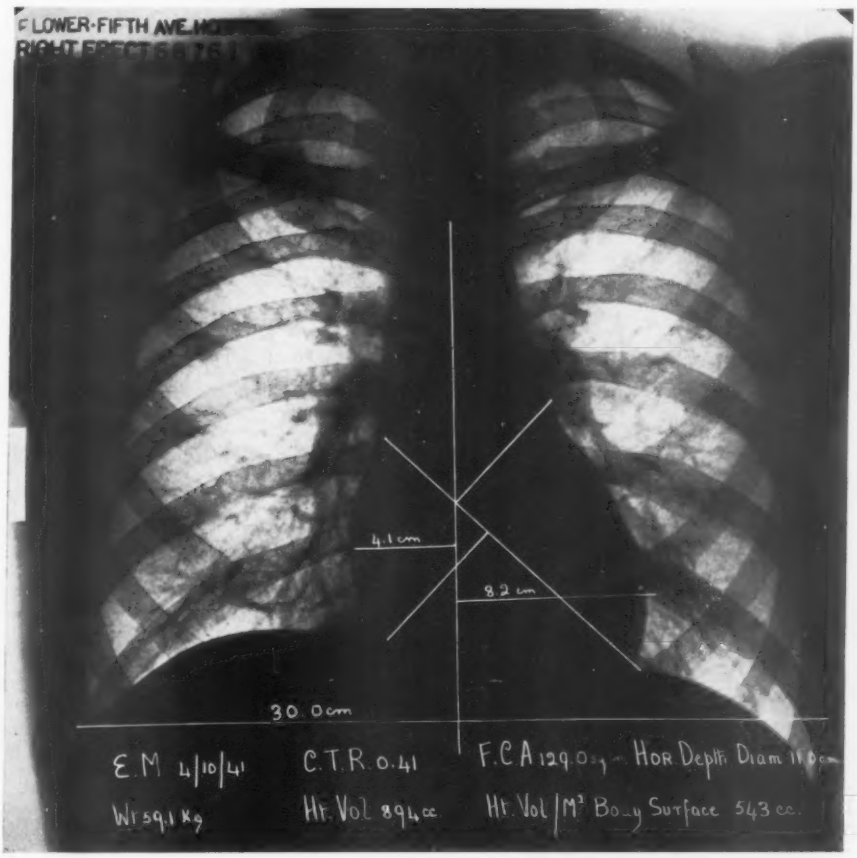

Fig. 2*B*.—Case E. M. Na = 1.5 Gm.; D = 30 mg.; and K = 45.

It is evident that the absolute values for either ingested sodium or desoxycorticosterone acetate, respectively, are not as important in influencing cardiac size in the treated patient as the interaction of the two in definite proportions. Ratios used in six patients and their relationship to the clinical condition of the patient have been recorded in detail elsewhere.[4, 5] Slightly different ratios are satisfactory in different patients, but in one and the same patient a nearly constant cardiac size can be *maintained* within limits on a constant product of sodium and desoxycorticosterone acetate according to the formula Na (Gm.) × D (mg.) = K, where Na represents the daily intake of sodium in grams, D is the daily dose of desoxycorticosterone acetate in milligrams, and

K is a constant. Variations from patient to patient in the value for K are inevitable and depend upon the degree of functioning cortex present in the given instance.

In four patients, the sodium and desoxycorticosterone acetate have been varied in relation to each other over considerable periods of time, in such a way, however, that the value for K in the above equation for a given series of observations has remained stationary. The results are recorded in Table IV and are illustrated by roentgenograms of patient E. M. (Fig. 2*A* and *B*).

TABLE IV

RESULTS OF VARYING SODIUM AND DESOXYCORTICOSTERONE ACETATE IN RELATION TO EACH OTHER WHILE THE PRODUCT REMAINS CONSTANT

(Each ratio of Na and D was used for a minimum of three weeks)

PATIENT	Na × D	DAILY INTAKE OF		C.T.R.	F.C.A. (SQ. CM.)	HEART VOL./ M^2 BODY SURFACE (C.C.)
		Na (GM.)	D (MG.)			
A. In Chronic Insufficiency						
K. K.	30	12.0	2.5	0.38	96.4	329
		6.0	5.0	0.39	101.8	338
		1.5	20.0	0.40	107.6	364
B. In the Fully Stabilized Patient						
K. K.	45	1.5	30.0	0.43	143.4	550
		3.0	15.0	0.46	129.0	530
E. M.	45	9.0	5.0	0.42	118.8	506
		6.0	7.5	0.42	115.4	532
		1.5	30.0	0.41	129.0	543
J. F.	45	9.0	5.0	0.45	112.0	506
		3.0	15.0	0.43	122.0	524
K. G.	45	6.0	7.5	0.41	101.3	442
		3.0	15.0	0.40	97.8	426

D, Desoxycorticosterone acetate; C.T.R., cardiothoracic ratio; F.C.A., frontal cardiac area.

DISCUSSION

One of the main problems in the satisfactory management of Addison's disease today is the establishment of reliable criteria by which the adequacy of treatment can be judged and by which complications may be avoided. Comment on criteria in common use will serve to show that they have too frequently been misleading, whereas the size of the heart has with one exception been informative.

1. *A Sense of Well-Being on the Part of the Patient.*—Until the use of desoxycorticosterone acetate, a sense of well-being was looked upon as one of the most useful criteria for gauging adrenocortical therapy. However, the recovery of the patient under the best of treatment is punctuated by periods in which he feels much as he did during the state of insufficiency or the impending crisis existing before therapy was started. The symptoms of such a state are also to be observed when too much desoxycorticosterone is being used.[6, 7] The difficulty is well

illustrated by Case K. G., who was first seen in impending crisis with nausea, vomiting, anorexia, recurrent abdominal pains, faintness, and extreme weakness. The blood pressure was 85/50; serum sodium and potassium were 273.2 and 8.5 mg. per cent, respectively. The patient was given a diet containing 3 Gm. of sodium and 6 Gm. of potassium daily, and a dose of 15 mg. desoxycorticosterone acetate daily.

At the end of three weeks, during which there had been steady improvement, nausea, vomiting, faintness, and weakness recurred. The blood pressure which had been above 100 was observed at 94/62; blood serum sodium and potassium were 344.7 and 11.8 mg. per cent, respectively. It was feared that these toxic signs were due to overtreatment until roentgenograms of the heart revealed a cardiothoracic ratio of 0.37, a frontal cardiac area of 82.0, and a heart volume per square meter of body surface of 366 c.c. When these values were compared with previous films of the chest, it was obvious that these measurements indicated cortical insufficiency. Therefore, the dose of synthetic hormone was raised to 20 mg. daily, whereupon the patient began again to improve. When the patient was fully stabilized some three weeks later, a maintenance dose of 15 mg. daily was established. Had this patient not been studied roentgenographically, the drug would have been discontinued or insufficiently used, and its use looked upon as a complete failure. Under adequate dosage, she has resumed her usual life, including attention to all her duties as a housewife.

2. *Gain in Weight.*—If the gain in weight is gradual, it may usually be looked upon as an indication of improvement. At times, however, and particularly if rapid, it may be misleading, as the retention of sodium and water resulting from overtreatment with desoxycorticosterone acetate also causes upward changes in the weight. Mrs. H. L. gained 3 kg. within sixteen days, during which time the blood pressure changed from 74/44 to 132/86; serum sodium and potassium, from 305.0 and 15.6, to 373.5 and 11.6 mg. per cent, respectively; the cardiothoracic ratio, from 0.35 to 0.58; the frontal cardiac area, from 75.6 to 143.0 sq. cm.; and the heart volume per square meter of body surface, from 328 to 693 c.c. During this period the intake of sodium was 10.7 Gm. daily, and the dose of desoxycorticosterone acetate, 10 mg. Gain in weight alone would have been no index to the severe intoxication with cardiac failure which was present at the time the second group of observations was made. While such an excessive increase in weight over a short period of time would lead one to suspect the rapid retention of water, there are many instances in which the change is less obvious and even misleading, unless other criteria, including cardiac size, are carefully considered.

3. *Rising or Normal Blood Pressures.*—The blood pressure level invariably improves in the patient under adequate treatment for Addison's disease. However, its fluctuations are sometimes marked, and in our

hands it has not consistently risen into abnormally high levels when the patient was being overtreated with desoxycorticosterone acetate. The case of Mrs. H. L., cited above, is illustrative. Just prior to the development of widespread edema of the ankles and early signs of cardiac failure, this patient showed a blood pressure of 132/86, normal for her age of 53 years. Again, Mr. J. F., a 60-year-old white male was "in good clinical condition" after several weeks of treatment. The blood pressure was 100/70; weight, 36.0 kg.; serum sodium and potassium, 327.1 and 16.8 mg. per cent, respectively; the cardiothoracic ratio, 0.45; the frontal cardiac area, 105.0 sq. cm.; and the heart volume per square meter of body surface, 494.6 c.c. The sodium intake was 3.0 Gm. daily, and the dose of desoxycorticosterone acetate, 20 mg. The latter was raised to 25 mg. daily in order to carry out some studies on glucose tolerance. Eighteen days later, the blood pressure was 116/72; weight, 41.6 kg.; serum sodium and potassium, 333.4 and 14.0 Gm. per cent, respectively; the cardiothoracic ratio, 0.51; the frontal cardiac area, 112.0 sq. cm.; and the heart volume per square meter of body surface, 507 c.c. There was some evidence of increased haziness of the perihilar shadows in the teleroentgenogram of the chest. The patient stated that he "felt fine." All features of his case were normal save for the changes in size of the heart, which were abnormally high. One week later he went into acute cardiac failure with pulmonary and peripheral edema while still on the same daily intake of sodium and desoxycorticosterone. At that time the blood pressure was 148/84; weight, 41.7 kg.; serum sodium and potassium, 332.7 and 16.4 mg. per cent, respectively; the cardiothoracic ratio, 0.55; the frontal cardiac area, 141.0 sq. cm.; and the cardiac volume per square meter of body surface, 675 c.c. It is apparent that blood pressure gave no forewarning of the impending complication in this patient. Cardiac size placed us on guard more than one week before clinical symptoms of disaster were in evidence.

4. *Normal Blood Sodium Levels.*—In our hands, blood sodium levels have been totally unreliable as an index to the adequacy of treatment. Kepler[8] expressed the same opinion. Patient K. K., observed for a little more than two years, was seen in crisis (two occasions), in cortical insufficiency, and in a fully stabilized state. The blood sodium values varied from 265 to 405 mg. per cent, but without any rational relationship to the clinical condition. On several occasions, when this patient was fully controlled, it was below 300 mg. per cent, and, at a time when he was feeling his best and all other prognostic factors were completely normal, the blood serum sodium was 284 mg. per cent. His status was satisfactory when the level was 405 mg. per cent, but he was far from as strong or subjectively comfortable as at the above period when the sodium was 284 mg. per cent.

5. *Improvement in the Blood Sugar Response to Ingested Glucose.*—With improvement in the patient's general condition, there is a return of the flat blood sugar curve to higher levels during the first three to four hours after oral ingestion of glucose. However, this relationship is not adapted to quantitative or mathematical expression.

6. *The Size of the Heart.*—This appears to be a reliable index of the clinical condition at all times.

That the size of the heart in patients with Addison's disease is profoundly influenced by the use of the synthetic hormone (desoxycorticosterone acetate) seems to be proved beyond question. Perhaps not one but a number of factors are responsible; the fundamental action of the drug is upon electrolyte metabolism. The retention of sodium with the concomitant binding of water and the stabilization of potassium equilibrium between cells and intercellular fluid appear to be of primary importance in bringing the heart back to normal size. When dosage is high enough to produce the toxic action, there is "packing" of the cells with sodium, and an increase above the normal in extracellular sodium chloride and water.* From periods of crisis through insufficiency to full therapeutic stabilization and toxic action, these effects of the hormone primarily vary inversely as the amount of sodium available within the tissues. In states of insufficiency without crisis and of full stabilization the relationship existing between the amount of sodium to be ingested and the amount of desoxycorticosterone acetate to be administered is capable of mathematical expression in terms of the previously described hyperbolic curve, $Na \times D = K$, in which values for K varying from 37.5 to 45 have been obtained in observations on seven human beings.[4, 5, 9] We believe a liberal supply of potassium (5 to 7 Gm. daily) should be available if the above equation is to hold, although the exact amounts necessary in any given instance have not been determined.

Only a limited portion of the hyperbola just mentioned can actually be employed in the regulation of the intake of sodium and desoxycorticosterone acetate. A satisfactory range for sodium is from 2.25 to 9 Gm. daily with concomitant inverse variations in desoxycorticosterone acetate from 20 to 5 mg. daily. Such large products for sodium and desoxycorticosterone are permissible only if our criteria for determining the condition of the patient are reliable. Therefore, we believe they should be used only when cardiac mensuration is performed repeatedly and systematically. In but one of 107 observations has the heart been within normal range of size when signs of toxicity from desoxycorticosterone were in evidence. In that instance, there was a moderate elevation of blood pressure and a very slight pretibial edema, both of which disappeared spontaneously without changing the patient's regime in any way.

*There is some evidence to show that such "packing" can be prevented if liberal quantities of potassium are made available. (Ferrebee, J. W. et al.: Replacement of Potassium by Sodium in Muscles of Normal Dogs Receiving Desoxycorticosterone Acetate. [Soc. Proc.], J. Clin. Investigation **20**: 445, July, 1941.)

Table IV clearly shows that the size of the heart is dependent upon the ratios of sodium and desoxycorticosterone acetate present and not upon the absolute value for the one or the other. Case E. M. (Fig. 2*A* and *B*) illustrates this perfectly. On Feb. 12, 1940, after several months of treatment with 6 Gm. of sodium and 7.5 mg. of desoxycorticosterone acetate daily the patient's cardiothoracic ratio was 0.42; the frontal cardiac area, 115.4 sq. cm.; and the heart volume per square meter of body surface, 532 c.c. On April 10, 1941, after a similar period of treatment with a daily intake of sodium of 1.5 Gm., and desoxycorticosterone acetate, 30 mg., the cardiothoracic ratio was 0.41; the frontal cardiac area, 129.0; and the heart volume per square meter body surface, 543 c.c. On both occasions, the patient was in good clinical condition, and the usual criteria of full stabilization were satisfied. However, the patient stated he felt better on the latter date when taking the larger dose of hormone, and concomitantly lessened amount of sodium. Within certain limits of dosage (up to 20 mg. daily) this patient's subjective appraisal can be made as a generalization for all of seven persons thus far observed.

Elsewhere, the dangers of high dosage with desoxycorticosterone acetate have been emphasized,[10-13] and precautions in their use have been stressed.[1, 4, 5, 9] Any one of the three heart measurements routinely employed in the present studies can be used as a reliable check to avoid overdosage. Suffice it to emphasize here the fact that, when the cardiothoracic ratio, which is extremely simple to determine, reaches or exceeds 0.50, a downward reduction in the dose of the synthetic hormone must be made if we wish to avoid a complication. The use of dosages represented on the hyperbolic curve, $Na = \frac{K}{D}$, by constants from 30 to 45, inclusive, has never produced such ratios. Therefore, such a range of values may be designated as the "zone of safe therapeutic constants."

In crisis or impending crisis, the uppermost of these constants can be safely exceeded, and here again therapy should be checked by cardiac mensuration as soon as the patient's general condition is sufficiently improved. We have used constants as high as 110 with values ranging from 11 Gm. sodium with 10 mg. desoxycorticosterone acetate to 5.5 Gm. sodium with 20 mg. desoxycorticosterone acetate). Such amounts should never be employed for more than three to four days without repeated determinations of the cardiothoracic ratio or other heart dimensions, for they have been known to cause acute cardiac failure within nine days of the time they were begun for the relief of crisis. In other words, while the usual equations for determining desoxycorticosterone and sodium intake in Addison's disease have constants which are much too low to be applied in the management of crisis or impending crisis, dosages indicated by higher figures must be discontinued as soon as the crisis is over. The condition appears to be comparable in every way to that

existing in diabetic acidosis and coma where the rules for insulin dosage in the controlled diabetic state no longer apply. The analogy may be carried one step further. There is some evidence[14, 15] to show that in diabetes the activity of insulin varies directly as the amount of glucose available in the blood and tissues, while in Addison's disease it seems well proved that the effect of desoxycorticosterone is proportionate to the sodium present. Sodium stores are depleted in crisis; hence, the need for higher ratios of ingested sodium and desoxycorticosterone acetate is obvious.

The Cause of the Small Heart in Addison's Disease and Its Increase in Size Under Desoxycorticosterone Therapy.—Our knowledge of the pathologic physiology involved in the alterations of the size of the heart in treated and untreated Addison's disease is meager, but in connection with the observations herein detailed, several facts may warrant attention. The previous[1] and present studies make it clear that adrenal insufficiency pathognomonically decreases the size of the heart, and that a still further reduction occurs, perhaps abruptly, when crisis is superimposed upon the already existing diminished function of the adrenal cortex.

The explanation for the sharp drop in cardiac size during crisis and for the early rapid restitution under treatment seems rather simple to explain on the basis of an encroachment upon blood volume.[1, 16] Similar downward changes in the size of the heart are seen with rapidly evolving, profuse diarrheas, excessive vomiting, severe hemorrhage, or any other condition in which there is a sudden, large drain upon body fluids. The fact that cardiac volume still remains from 15 to 20 per cent below the theoretical normal following the relief of crisis[1] while blood volume is restored to normal promptly is prima facie evidence that the volume of circulating blood seen in adrenal insufficiency is not alone responsible for the small heart routinely present.

Changes in water and electrolyte balance undoubtedly play a considerable role in bringing about the changes seen in the disease and in re-establishing normal conditions during treatment.[17-20] During adrenal insufficiency, water and potassium are both lost from muscle tissue, although the proportion of potassium to dried weight of the muscle remains as in the normal animal.[21, 22] Sodium stores of the body are depleted, and the amount of potassium in the intercellular fluid and in the blood stream increases. While other changes are concomitantly present, the above alterations in electrolyte pattern are outstanding.

Whether the role of sodium, potassium, and water is a truly primary or purely secondary one in the production of the small heart of Addison's disease is as yet not entirely clear. The influence of the cortex upon carbohydrate metabolism is also a profound one. Glycogen reserves in the liver and in the heart are markedly reduced. Fenn has recently cited the literature on this point.[24] When glycogen leaves the muscle,

potassium goes with it.[16, 23, 24] It is difficult to say whether the status of muscle glycogen or of cell potassium is altered first. The evidence seems to favor the view that potassium is a basal factor in the syndrome of corticoadrenal insufficiency.[25-29] Moreover, there is evidence to show that the action of the potassium on the heart is at least to some extent a specific effect not shared by skeletal muscles generally.[30]

When we turn from the findings of adrenal insufficiency to the other side of the picture, that is, to the absolute and relative increase in the size of the heart in the patient under treatment for Addison's disease with desoxycorticosterone acetate, perhaps conclusions may be drawn with more certainty. Under the influence of this steroid, there is an increase in intracellular water and potassium, and a decrease in extracellular water and chloride, until such time as intoxication begins when the two latter factors increase above the original values. The handling of purely carbohydrate food is improved[31, 32] probably through the general improvement in the state of the animal and through no direct influence upon processes fundamental to intermediary sugar metabolism.[33-35] This improvement and a return of cell potassium to normal may combine to afford the heart a better glycogen reserve.

If the several facts cited above and assumptions based upon them are true, then the diminished size of the heart in Addison's disease is primarily a result of the loss of cellular glycogen, potassium, and water, and the restitution of size under desoxycorticosterone acetate is associated with a re-establishment of potassium and water balance with a concomitant improvement in glycogen stores.

SUMMARY

1. One hundred seven observations have been made upon the size of the heart in seven cases of Addison's disease under treatment with desoxycorticosterone acetate.

2. Cardiac size has been indicated by estimations of the cardiothoracic ratio, the frontal cardiac area, and the heart volume.

3. These measurements of cardiac size have been correlated with the clinical condition of the patient and with the intake of sodium and desoxycorticosterone.

4. The present criteria for indicating the condition of the patient with Addison's disease have been critically evaluated.

5. Rules for applying desoxycorticosterone therapy have been discussed.

CONCLUSIONS

1. In patients under treatment for Addison's disease the size of the heart increases as the clinical condition improves.

2. The first and most reliable sign of toxicity from desoxycorticosterone acetate is an abnormally large cardiac silhouette in the teleroentgenogram.

3. A reduction in the dose of hormone is advisable if the cardiothoracic ratio reaches 0.50 or above.

4. Large doses of hormone may be given with safety when cardiac mensuration is used as an objective check on the clinical condition.

5. The dose of desoxycorticosterone acetate necessary to produce a given degree of cardiac enlargement varies inversely as the amount of sodium available in the tissues.

6. The dose of desoxycorticosterone acetate should be regulated according to the formula, Na (Gm.) $\times$ D (mg.) $=$ k. Values for k of from 30 to 45 have been ascertained in a prolonged study of seven patients with Addison's disease.

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Department of Clinical Reports

COMPLETE HEART BLOCK ALTERNATING WITH NORMAL RHYTHM AND NORMAL A-V CONDUCTION

Report of Two Cases

J. Morrison Hutcheson, M.D., and Wellford C. Reed, M.D.
Richmond, Va.

FROM the paucity of reference to the condition in textbooks on cardiology and from the small number of cases recorded in the literature, it may be inferred that complete A-V dissociation, interrupted by periods of normal rhythm and normal conduction, is rare. For this reason the following cases are reported. Both show Adams-Stokes seizures and both illustrate the tendency, previously noted in such cases, to develop permanent block with the disappearance of attacks.

CASE REPORTS

Case 1.—A lawyer, aged 67 years, was admitted to the Johnston Willis Hospital July 10, 1938. His chief complaint was fainting spells, which had occurred at irregular intervals and with increasing frequency for two years. The first attack occurred in July, 1936, while he was sitting engaged in conversation and lasted thirty seconds. About two months later he had a second attack and consulted a physician, who took an electrocardiogram and found no evidence of heart block, although this had been suspected. In May, 1938, attacks began to come while he was lying in bed, and one week before admission he had seven in one day. The seizures were always preceded by a feeling that the blood was leaving his head, and occasionally he seemed able to prevent them by getting down on hands and knees or by holding his head between his knees. Some attacks consisted only of faintness, while in others he became unconscious, with convulsive shaking of the body and extremities. Once, when examined during an attack, he was told that his pulse rate was 26. For a number of years he had grown progressively short of breath and had slight swelling of the ankles, but at no time had he noticed chest pain.

Physical examination showed a fairly obese man of florid complexion, 5 feet 6 inches tall and weighing 172 pounds. The pulse was regular, 40 to the minute. Blood pressure was 178/105. The heart was enlarged to the left; the aortic second sound was accentuated with a soft blowing systolic murmur at the apex. Extra sounds were heard between regular beats, and extra pulsations were seen in the neck veins. The lung bases were clear; the liver not enlarged; and only very slight pitting of the ankles was observed. Laboratory studies, including Wassermann, were essentially negative. An electrocardiogram taken a few hours later revealed normal

From the Medical Service, Johnston Willis Hospital, and the Hospital Division of the Medical College of Virginia.
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rhythm and normal conduction (Fig. 1). On the following day, although there had been no attacks, complete dissociation was present (Fig. 2). He remained in the hospital until July 31 and had a number of fainting spells and several convulsions. These were without apparent exciting cause. Efforts to obtain a tracing during an attack proved futile as the string was deflected by body movements. Atropine had no effect nor did carotid sinus pressure influence the rhythm. Ephedrine in large doses appeared to diminish the number of attacks but caused slight

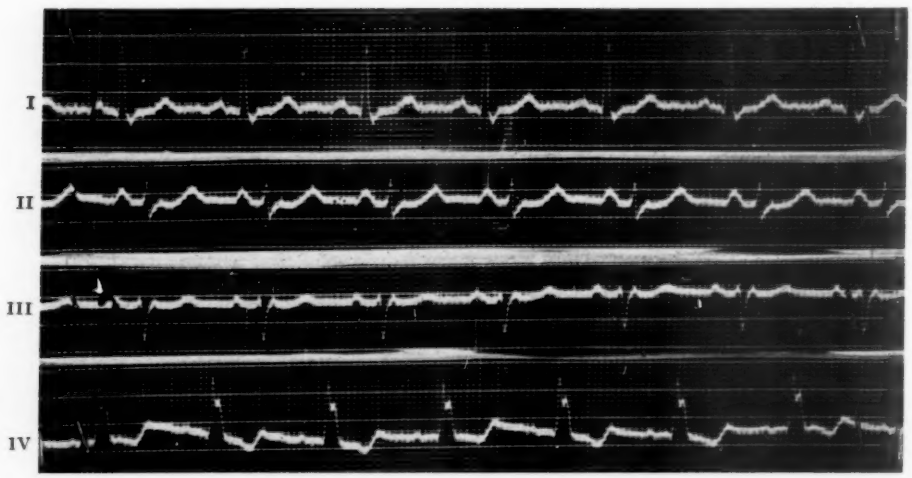

Fig. 1.—Case 1. Normal rhythm with normal A-V conduction.

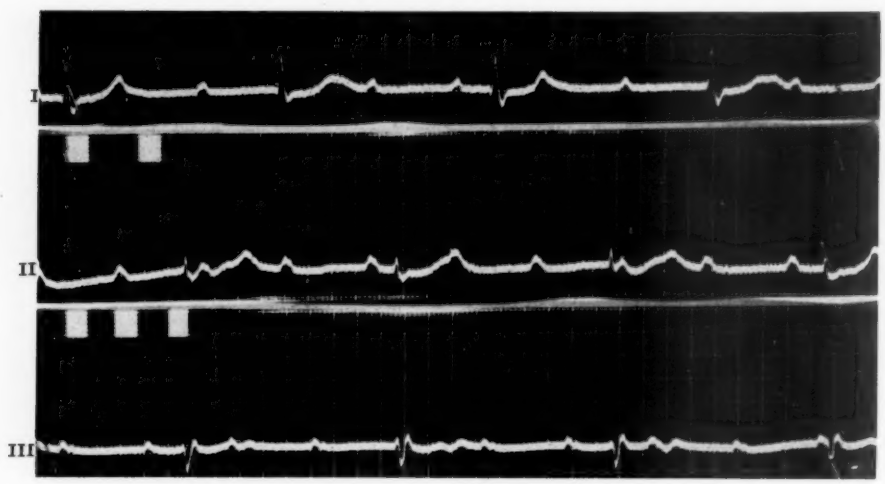

Fig. 2.—Case 1.—Complete A-V dissociation.

nervousness. On discharge he was advised to take ¾ grain ephedrine with one zanthimal tablet (theophylline and phenobarbital) every three hours when awake. This therapy was continued, and, when he was seen at the office October 3, he stated that he had had only one mild attack since August 4. At that time he showed a complete block. On December 5 he had several attacks and complete block was found. On Jan. 23, 1939, he stated that there had been no attacks in ten days.

Normal rhythm with a pulse rate of 76 was present at this time. On March 6 he reported about one mild attack a week, and on that day complete block was found. In September, 1939, attacks ceased and complete block later appeared to be persistent. Dyspnea and other evidence of congestive failure appeared, and after November, 1939, he was digitalized. On June 11, 1940, he showed evidence of mild congestive failure but was able to perform his duties as judge of a local court. Complete block was present, and digitalization had produced no measurable change in the electrocardiogram. On July 11, 1940, he died suddenly. Permission for autopsy was not secured.

CASE 2.—A married woman, aged 58 years, was admitted to the Memorial Hospital Dec. 18, 1939, complaining of high blood pressure of eight years' duration and fainting spells. Except for occasional severe headache, she had been generally well up to May, 1939, when she began to have fainting spells. These seemed to follow moderate exertion. During the spells she was unconscious for a few minutes. In two attacks she fell and struck her head. After the third attack her right arm and leg became paralyzed, but later she recovered the use of both limbs. Following this illness she was breathless after exertion and had occasional mild nocturnal dyspnea of paroxysmal character. For several months she had been having a different type of attack, which she described as "swooning." She would first notice a feeling as if her heart were turning over and almost immediately a sense of faintness, but she did not lose consciousness. The attacks bore no relation to meals or exertion.

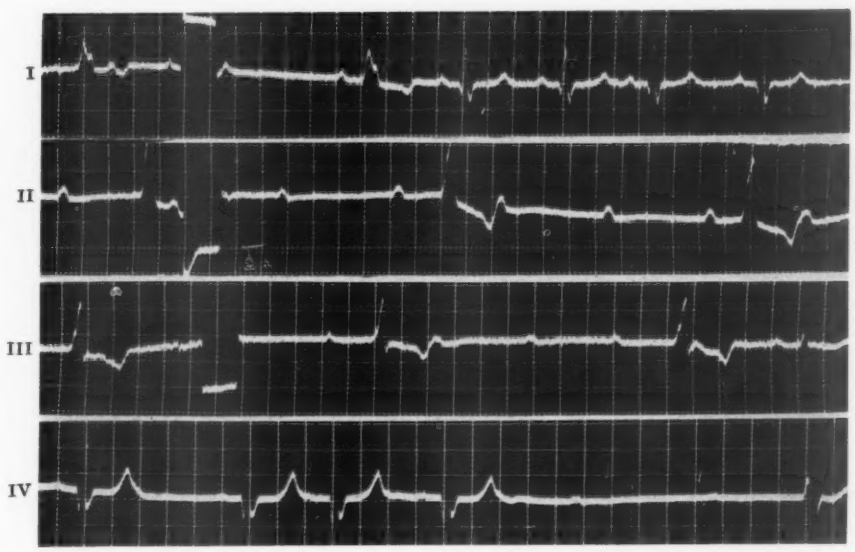

Fig. 3.—Case 2.—Complete A-V dissociation with a short period of sinus rhythm in Leads I and IV.

Examination on admission showed a regular pulse (30 per minute) and blood pressure of 180/90. The heart was markedly enlarged to the left, and a fairly loud systolic murmur was heard over the apex. A few basal râles were noted, and there was slight pitting edema of the ankles. Laboratory examinations of blood and urine showed nothing of interest. The electrocardiogram revealed complete A-V dissociation with bundle branch block and, in one record, occasional brief runs of normal rhythm and normal conduction (Fig. 3).

While in the hospital she continued to have frequent attacks. The nurse's note indicated that she would have a warning that an attack was imminent and at this time the pulse would change from the usual slow rate to 90 or above. Her face would become flushed; she would perspire profusely; and at the same time a long pause might be observed in the pulse beats, followed by a return to the slow rate. Atropine and ephedrine failed to influence the heart rate or the frequency of attacks. On December 25 the administration of benzedrine sulfate, 5 mg. three times a day, was begun and on the same day the rhythm became normal with normal A-V conduction (Fig. 4). Benzedrine was discontinued Jan. 3, 1940, but the rhythm remained normal, and there were no further attacks. She was discharged on Jan. 25, 1940. Correspondence with her physician revealed that normal rhythm persisted for two weeks after she returned home. She then began to have periods of complete block with unconscious seizures. Benzedrine sulfate was given again but was not definitely useful. Since about June 14, 1940, complete block has apparently been maintained, and there have been no attacks.

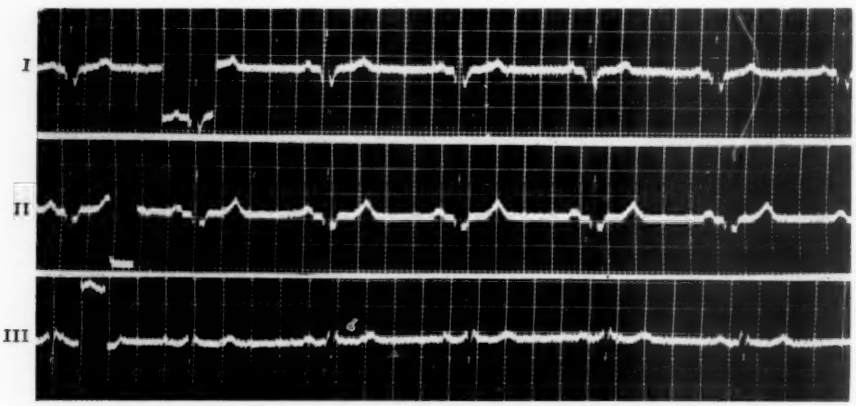

Fig. 4.—Case 2. Normal sinus rhythm.

COMMENT

Comeau[1] in 1937 was able to collect from the literature only twelve cases in which it was clearly established that a sudden transition from normal conduction to complete block with idioventricular rhythm actually occurred. To this group he added two additional cases, in one of which Adams-Stokes seizures ceased after complete block became permanent. Of particular interest in the cases here recorded are the frequent Adams-Stokes seizures, which apparently followed the shift from normal rhythm to block. In both cases the aura and in Case 2 the nurse's description of the attack and the electrocardiogram suggest that a brief run of normal rhythm occurs and the unconscious attack comes during the pause after the cessation of normal rhythm and before idioventricular rhythm begins. Both cases showed evidence of bundle branch block, which varied in degree from normal rhythm to complete block, becoming more marked in the latter. In Case 1 ephedrine in large amount seemed to diminish the number of syncopal

attacks. In Case 2 normal rhythm appeared soon after benzedrine was given and persisted for six weeks after the drug was stopped. Although it seemed unlikely that the transition was induced by the drug, the observation is of interest as Poole and Wilkinson[2] have reported a similar case, in which reversion to normal rhythm appeared to follow small doses of benzedrine.

Since both patients were past middle age and had hypertension and since the presence of electrocardiographic changes indicated myocardial damage, it may be concluded that the underlying pathology was cardiosclerosis.

SUMMARY

1. Two cases showing complete A-V block with alternating periods of normal rhythm and normal conduction time are reported.

2. In both cases frequent Adams-Stokes seizures occurred during the period of fluctuating rhythm.

3. In one case definitely and in the other probably, permanent A-V dissociation was eventually established with the disappearance of syncopal attacks.

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ANOMALOUS CORONARY ARTERIES ARISING FROM THE PULMONARY ARTERY

Report of a Case in Which the Left Coronary Artery Arose From the Pulmonary Artery

Louis A. Soloff, M.D.
Philadelphia, Pa.

REPORTS of abnormalities of the coronary arteries in which one or both arise from the pulmonary artery are rare. A majority of the cases present a fairly characteristic clinical syndrome which should probably make antemortem diagnosis possible. Furthermore, with the increasing interest in, and growing importance of, coronary artery disease, all abnormalities of the coronary arteries are noteworthy. In these types of cases, one can learn, with almost the precision of a physiologic experiment, whether irrigation of portions of the myocardium with venous blood under low pressure is adequate to maintain its functional and anatomic integrity and, if it is not, how the heart successfully circumvents this abnormality or succumbs to it. The purpose of this paper is to report a case which presented an anomalous left coronary artery arising from the pulmonary artery with degenerative changes in the left ventricle resulting in an aneurysmal dilation of this chamber and an incidental persistence of the embryonic sinusoids and also to review the literature on anomalous coronary arteries arising from the pulmonary artery.

REPORT OF A CASE

F. P., a male infant, aged 4½ months, was admitted to the St. Joseph's hospital Oct. 13, 1940, at 7:00 P.M. and died the following morning before any studies could be made. The child was born, full term, at home, of normal parents. The infant was apparently normal at birth, but soon thereafter he began to regurgitate his food. He was brought to the pediatric clinic where the formula was changed twice with some improvement. Five days before admission to the hospital, with each feeding, the child apparently expressed severe pain by doubling up, drawing his feet up to his chest, holding himself tense and motionless and becoming cyanotic. After a few moments, he vomited his food, became pale, and perspired. Since these attacks began, the child was able to take less and less of his food without precipitating an attack. During the last two or three days, he had become visibly short of breath.

Physical examination in the hospital revealed an emaciated, slightly cyanotic, dyspneic infant with a respiratory rate of 52 a minute. There was a marked diminution of respiratory excursion on the left side anteriorly and posteriorly. No

From the Department of Medicine, Temple University Medical School.
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râles were audible. The heart sounds were normal but rapid. The provisional diagnosis was atelectasis of the left lung. The child died the following morning before x-ray or other studies could be done.

Necropsy.—Autopsy was done five hours after death. There was a moderate cyanosis of the lips, fingernails, and toenails. The anterior-posterior diameter of the chest exceeded the transverse diameter; this gave the appearance of a barrel-shaped emphysematous chest. Aside from the heart, nothing of note was found except for the adrenals and lungs. The adrenals revealed medullary hemorrhage. The lungs had several small atelectatic regions which were greatest in size and number in the left upper lobe.

Fig. 1.—Anterior view of the heart illustrating aneurysmal dilatation of the left ventricle and the huge engorged veins.

The pericardium in situ was tremendously distended. It extended 3 cm. to the right of the midsternal line and to the left mid-axillary line so that the entire left lower lobe and a portion of the left upper lobe of the lung were obscured from view. When the pericardial sac was opened, its distention was seen to be due entirely to a huge heart. The transverse diameter of the heart was 11 cm. The left lower pole of the heart was formed entirely by the left ventricle. The interventricular groove was situated 2 cm. from the left lower pole. Numerous tremendously dilated veins were present beneath the epicardium of the left ventricle. These were largest at the base of the heart where they varied in size up to 1.2 cm. in diameter, and projected above the muscular surface for as high as 1 cm. The lower half of the left ventricle bulged ventrad, to the left and craniad in an obvious aneurysmal dilatation. The ventricular muscle in this region felt extremely thin and easily compressible. The right ventricle appeared normal. The external appearance of the heart was identical with that as is frequently seen in an acute coronary thrombosis superimposed upon an aneurysmal dilatation of the left ventricle secondary to an old coronary thrombosis. The difference was the markedly dilated and engorged coronary veins. The section surfaces of the right ventricular muscle were normal. The section surfaces of the left ventricle muscle were obviously diseased. Practically no normal healthy muscle was seen. Large regions of gray fibrous tissue alternated with dull brown muscular tissue and regions of apparently acutely necrotic tissue. One

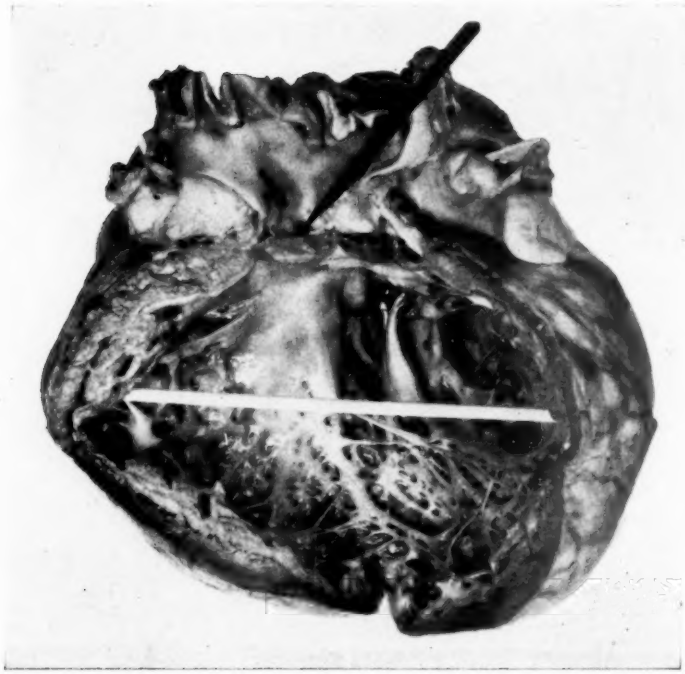

Fig. 2.—A view of the left ventricular cavity illustrating the normal origin of the right coronary artery, the necrotic muscular wall, and the hypertrophied trabeculae carneae.

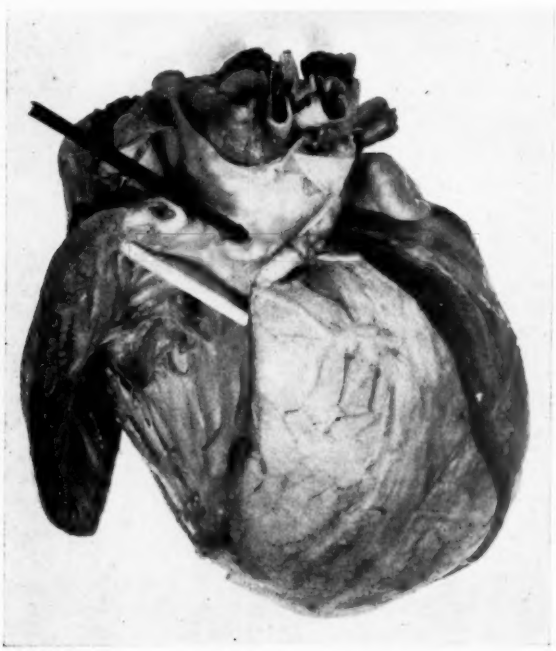

Fig. 3.—The anomalous origin of the left coronary artery arising from the pulmonary artery and the comparatively small normal right ventricle.

could also see numerous large, engorged blood vessels and tiny empty spaces, the nature of which was not suspected until microscopic examination. The valves were all normal. After fixation in 10 per cent formalin, the aortic valve was 4 cm. in circumference; the pulmonary, 3 cm.; the mitral, 5 cm.; and the tricuspid, 7 cm. The right coronary artery arose at its usual site from the aorta. The ostium was approximately one-half its normal size. The left coronary artery arose from the pulmonary artery. The orifice was approximately three times that of the right coronary artery. So far as one could tell by dissection with fine scissors, the distribution of the coronary arteries was normal. The right coronary artery supplied the greater portion of the right ventricular wall and a small portion of the posterior basal portion of the left ventricle. The left coronary artery, by means of its usual two major branches, supplied virtually the entire left ventricular muscle, its finer ramifications being lost in the diseased muscle. No communications could be discovered between the major branches of the coronary arteries or between the coronary arteries and veins. The heart weighed 120 Gm. The normal for this age is approximately 30 Gm.

Fig. 4.—Left ventricular muscle illustrating necrosis, fibrosis, and calcification.

Histologic examination of the heart revealed pathology confined to the left ventricle. The right coronary artery was normal. The left coronary artery was wider than normal, but its wall was thinner than normal and thinner than the right. This was due essentially to the thinness of the media which gave the vessel the appearance of a vein except for the presence of a distinct internal elastic membrane. In the left ventricular myocardium very few coronary arterial branches

could be seen. Instead, there was an abundance of two distinct types of vessels. One type was obviously a vein. The larger ones were normal. The smaller ones were surrounded by a thick hyalinized zone of connective tissue. In many regions this zone was thicker than the entire enclosed vessel. The other type of vessel varied in size from a tiny cleftlike space to that occupying a low-power field. It was composed of a single row of flat endothelial cells. The vessels were either empty or filled with red blood cells. In some of these regions, the muscle cells were less compact than normal and resembled late embryonic heart muscle. These vessels were obviously persistent embryonic sinusoids, an interpretation which was concurred in by several outstanding pathologists to whom these sections were shown. Very little normal muscle was seen. All stages of degeneration were present. There were acute parenchymatous degeneration, hydropic degeneration, fatty degeneration, ischemic necrosis, fibrosis, and calcification.

Fig. 5.—The persistence of the embryonic sinusoids.

DISCUSSION

The possibility of the origin of the coronary arteries from the pulmonary artery is due to the fact that the primitive endothelial buds which are to form the coronary arteries develop before the common arterial trunk is divided by the spiral septum into the aorta and pulmonary artery. A displacement of either the endothelial buds or the spiral septum may enclose one or both endothelial buds within the pulmonary artery. Four possibilities exist: (1) origin of the right coro-

nary artery from the pulmonary artery, (2) origin of the left coronary artery from the pulmonary artery, (3) origin of both coronary arteries from the pulmonary artery, and (4) origin of an accessory coronary artery from the pulmonary artery. The last possibility is of little importance, inasmuch as the accessory artery usually corresponds to a small branch of the coronary artery and supplies but a limited portion of the myocardium. References to this anomaly are given by Bland, White, and Garland. There have been sixteen previous reports of the left coronary artery, two of the right coronary, and two of both coronary arteries arising from the pulmonary artery. The much greater frequency of the left coronary artery arising from the pulmonary artery has been attributed to the fact that the ostium of the left coronary artery is much closer to the pulmonary sinus than is that of the left. Another believed that the greater incidence has no statistical significance because of the small number of cases.

Of the sixteen persons with an anomalous left coronary artery, eleven died in infancy between the third and fifth month and one died at the age of 10 months. The histories were all very similar. The children were born normally at term. They were apparently healthy. Soon after birth, they began having trouble with feedings.

At first there was regurgitation of food. A little later, dyspnea was present during feedings, usually accompanied by slight cyanosis. Soon thereafter, symptoms suggestive of pain occurred followed by perspiration and shock. Because all of the symptoms occurred at first only during the act of swallowing, it is very probable that these infants suffered from angina pectoris. Later symptoms of respiratory distress occurred even when the child was at rest. This gave rise to symptoms suggestive of pneumonia, which was the usual antemortem diagnosis. X-ray examination revealed a large heart. Only one case had an electrocardiogram, which showed a well-marked and late inversion of the T waves in all leads of the coronary type. The report of this last case of Bland, White, and Garland should be read for the excellent description of the paroxysmal attacks which were observed by the child's father, who was a physician. At autopsy all cases showed an enlargement of the heart, usually two to three times the normal size, with predominant enlargement of the left ventricle which had a typical aneurysmal bulge in its caudal and lateral half. Microscopically, degeneration in every way resembles the ischemic myocardial degeneration and fibrosis of coronary sclerosis except that it is more intense, more widespread, and more confluent. Heitzmann was the first to be impressed by this similarity. In order to test this similarity, a colored photograph of the heart and several microphotographic sections of the muscle were shown to several cardiologists without giving them any clinical data. The invariable diagnosis was myocardial infarction with aneurysmal dilatation of the left ventricle due to coronary thrombosis.

EMBRYONIC SINUSOIDS

The myocardium in this case differed in one respect from the heart muscle of all the other cases reported. There were numerous large and small distended and cleftlike spaces partly filled with red blood cells and lined by a single row of flat endothelial cells. These were not capillaries of the type seen proliferating in granulation tissue. They were distinctly different, as evidenced by their shape, their size, and their presence in regions where the muscle was healthy although apparently slightly embryonic. The embryonic myocardium, before the development of the coronary vessels, is nourished by blood coursing through spaces between the interlacing muscle fibers. These spaces communicate freely with the ventricular cavity. Grant, in his studies on the development of the cardiac coronary vessels in the rabbit, has shown that these spaces are reduced to capillaries by the condensation of the myocardium and persist to form an integral part of the coronary circulation. Those in the vicinity of the endocardium persist in their communications with the ventricular cavity and form the veins of Thebesius. This is the third case of persistence of the embryonic sinusoids which could be found, and it is interesting to note that the sinusoids were inadequate to prevent the degenerative changes of the myocardium.

Four of the sixteen persons lived to adulthood. Abbott's patient died accidently at the age of 64 years. The descending branch of the left coronary artery expanded into a large triangular-shaped sinus which communicated with large thick walled vessels behind it. Rubberdt's patient was a man 27 years old who had been examined three weeks prior to his death and was pronounced healthy. He died suddenly while doing hard work. The right coronary artery was tremendously dilated and was the size of the iliac artery, 3.1 cm. in diameter. The right coronary artery anastomosed freely with the left. Kockel's patient was a man 38 years old who had had precordial pain for a few years. The heart was enlarged. There was a sclerotic patch in the bundle of His. The right coronary artery was huge. The left was larger than normal. Both coronary arteries extended to the apex of the heart. The right had apparently taken over some of the function of the left, and there were apparently anastomoses between the smaller branches of these vessels. Dietrich's patient lived to the age of 57 years. He was reputed to have been sick as a child, but adolescence was normal. Upon applying for army service, he was told that he had valvular heart disease. For ten years previous to his death he had hypertension, auricular fibrillation, and angina pectoris. Autopsy revealed aortic valvular disease and a large heart. The right coronary artery was atherosclerotic. The left, which arose from the pulmonary artery, was not atherosclerotic. There were numerous large regions of calcification. In the smaller branches of the left coronary artery and its arterioles were

invaginations of the arterial wall into the lumen which Dietrich had never seen in atherosclerosis. These findings were quite similar to those seen in the glomus tumors of the fingers; he regarded them as conclusive evidence of arteriovenous anastomoses. Injections of radiopaque substance failed to show any communication between large vessels; this was not conclusive since the heart had been previously partly dissected.

To summarize the cases of anomalous left coronary arteries arising from the pulmonary artery, the clinical history is that of an infant, apparently normal at birth, who develops usually in the third, fourth or fifth month, with the onset of active motion, difficulty in feeding, with regurgitation, dyspnea, cyanosis, pallor, sweating or shocklike countenance precipitated by the effort of eating. X-ray examination reveals a large heart. Careful fluoroscopic examination should demonstrate an aneurysmal bulge of the left ventricle. The only electrocardiogram, that of Garland et al., shows the typical coronary T wave changes which one should expect from the state of the myocardium. Life is possible if adequate anastomoses are present between the coronary arteries or between the left coronary artery and the ventricular cavity. Otherwise the retrogressive changes of tissue anoxia are too extensive to permit normal function of the left ventricle. In those cases with adequate anastomoses, symptoms may be entirely absent. Sudden death may occur. The finding of focal calcifications in the myocardium (by x-ray examination) without apparent cause in an adult should suggest this possibility. From a pathologic standpoint, it is interesting to note the differences in appearance of the left and right coronary arteries. The left coronary artery, although wider than normal, has a wall distinctly narrower than normal, due primarily to a poorly developed medial muscular coat. This suggests that the muscular coat develops in response to the increased pressure within the lumen and explains the increased thickness of this coat found so frequently in persistent hypertension. The presence of atherosclerosis in the right coronary artery and its absence in the left also point to the relation of increased work and pressure to the pathologic changes in the walls of the arteries. Such a relationship is similar to the phlebosclerosis of the inferior vena cava seen in long-continued chronic passive congestion.

Only two cases of an anomalous right coronary artery arising from the pulmonary artery have been reported. In contrast to the left, both were adults who died of unrelated disease. Moenkeberg's patient was a male 30 years old who died of an epileptic fit with a fracture of the scapula and a dural hemorrhage. Schley's patient was a syphilitic man 61 years of age. In contrast to the cases with anomalous left coronary arteries, no significant pathologic changes were found in the myocardium. In these cases the right coronary artery was thin walled and

of venous character. The absence of anatomic changes in the myocardium and the absence of symptoms were attributed to adequate collateral circulation between the coronary arteries. This, however, was merely an assumption as it was not demonstrated in either case. One cannot draw a generalization on the basis of two cases. It appears unlikely that collateral circulation is more likely to occur from the left to the right coronary artery than the reverse. The explanation suggested by Linck seems more plausible. The left ventricle has more work to do and hence requires more oxygen. The oxygen content of the venous blood is adequate for the right ventricle and not for the left. It is interesting to note that, although sclerosis occurs frequently in both coronary arteries in the adult, ischemic fibrosis is rare in the right ventricle, whereas it is common in the left.

There are only two cases reported in which both coronary arteries arose from the pulmonary artery. Grayzel and Tennant's patient was a 10-day-old female with associated congenital atresia of the tricuspid orifice and interventricular septal defects. No histologic description of the myocardium is given. Limbourg's patient was also a 10-day-old infant who developed cyanosis and dyspnea after the third day. X-ray examination revealed a large heart. Autopsy disclosed tentorial tears and a large heart due predominantly to a huge left ventricle. Microscopic examination of the myocardium revealed fat droplet (hydropic?) degeneration equally present in both ventricles. Unfortunately, no illustrations of the myocardium are given. The impression obtained from reading this paper is that the histologic changes were meagre although grossly there was a disproportionate increase in size of the left ventricle.

COMMENT

From this review, it would appear that the origin of both coronary arteries from the pulmonary artery is incompatible with life beyond infancy, that the origin of the right coronary artery from the pulmonary artery is compatible with health and is asymptomatic, and that the origin of the left coronary artery from the pulmonary artery is compatible with health in the presence of an adequate collateral circulation. In the absence of an adequate collateral circulation, this anomaly gives rise to a clinical picture characterized by angina pectoris, particularly precipitated by feeding, and left ventricular failure. Anatomically (roentgenologically) a huge heart with aneurysmal dilatation of the left ventricle is found. The electrocardiogram taken in one case showed a late deep inversion of the T wave in all leads. These symptoms appear most commonly in the second or third month of life, and death usually occurs in the third to the fifth month.

SUMMARY

1. A case in which the left coronary artery arose from the pulmonary artery is described.

2. The literature of anomalous coronary arteries arising from the pulmonary artery is reviewed.

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C. Origin of Both Coronary Arteries From the Pulmonary Artery

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D. Persistence of Embryonic Sinusoids

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Department of Reviews and Abstracts

Selected Abstracts

Nonidez, J. F.: Studies on the Innervation of the Heart. II. Afferent Nerve Endings in the Large Arteries and Veins. Am. J. Anat. 68: 151, 1941.

The composition of the aortic nerve and the distribution and structure of the aortic pressoreceptors are first considered. It is pointed out that some of the afferent fibers are very thin and give rise to terminations which lack the reticular swellings observed in the arborizations of the larger fibers (Fig. 3). These terminations, however, are regarded as pressoreceptors since they do not occur elsewhere in the aorta, left subclavian and innominate arteries. It is suggested that they are probably the last ones to cease functioning when the blood pressure reaches the 200 mm. Hg level.

The terminations in the arterial ligament are discussed in the light of the work of Takino and Watanabe, who believe that they function during fetal life. This is questioned because the physiologic activity of the pressoreceptors requires a level of blood pressure are not reached until post-natal life. It is also pointed out that some of the nerve endings in the ligament are probably terminations of parasympathetic postganglionics; this would explain the contraction of the ductus arteriosus observed by Barcroft and co-workers in guinea pig fetuses upon excitation of the left vagus.

The complexity of the receptors in the large veins increases with age. In a general way they appear more scattered than in the younger animals. The endings in the superior and inferior venae cavae persist after cervical and upper thoracic sympathectomy in the cat (Fig. 4), but the subendothelial and perimuscular endings in the pulmonary veins degenerate. This proves that the caval receptors belong to afferent fibers coursing in the vagus, but does not offer conclusive evidence as to the course followed by the fibers ending in the pulmonary veins because of the presence of vagosympathetic anastomoses.

In the pulmonary veins of puppies there are two types of afferent endings: (a) flattened arborizations located immediately under the endothelium (Fig. 5); and (b) more compact arborizations with large swellings in their branches, situated in the subendothelial layer (Fig. 6).

The role of the nerve arborizations in the pulmonary veins is taken up in connection with the researches of Daly and his co-workers on the existence of receptors in the pulmonary vascular bed. The question of the existence of receptors responsible for the pressor effects observed by McDowall and, more recently, by De Waele and Van de Velde is also considered, and it is suggested that the afferent fibers for these reflexes run in the sympathetic as well as in the vagus.

Other afferent nerve endings present in the externa of the arteries (Figs. 7 and 8) are briefly considered.

AUTHOR.

Smith, A. L.: Stethogram and Recorded Disc of Fetal Heart Sounds in a Twin Pregnancy. Am. J. Obst. & Gynec. 42: 908, 1941.

A stethogram of twin fetuses and the disc recording of these heart sounds, which could be audited when desired, are reported.

A twin pregnancy in which there was a question of viability of one fetus is described.

The stethogram and recorded disc of the twin fetal heart sounds made the positive diagnosis of two live fetuses, and this was confirmed by the birth of two normal babies.

This is believed to be the first stethogram and disc recording of twin fetal heart sounds reported in medical literature.

AUTHOR.

Smith, A. L.: Recording and Reproduction of a Fetal Heart Murmur Confirmed After Birth. Arch. Pediat. 58: 549, 1941.

It is believed this is the first report in the medical literature of a fetal heart lesion recorded in a stethogram or on a phonographic disc.

It is believed that a diagnosis of prenatal heart lesions can be made by either method.

In this case the prenatal diagnosis of a heart lesion was confirmed after birth and one year later.

AUTHOR.

Smith, A. L.: Confusion in Differentiation of Heart Murmurs and Sounds. J. Kansas M. Soc. 42: 457, 1941.

Murmurs may occupy any part of or be continuous throughout the cardiac cycle.

Murmurs of organic or inorganic heart origin, of intracardiac or extracardiac origin, and murmurs of all types and the various other heart sounds are often confused. This oftentimes results in unnecessary treatment or lack of necessary treatment, much to the detriment of the patient in either case.

This confusion can be prevented in most of these cases by the employment of accurate cardiac instruments.

Murmurs in themselves are no disease and need no treatment but, when accurately diagnosed, point to the underlying cause which often can be eliminated.

The earlier the recognition of the murmur and its cause, the earlier proper treatment may be instituted.

The advancement of methods of auscultation and the accurate registration of heart sound findings have increased our knowledge of the heart, but all other methods of any value must be used, as well, to arrive at a complete, accurate understanding of the condition of the heart.

AUTHOR.

Butterworth, J. S., and Poindexter, C. A.: Short P-R Interval Associated With a Prolonged QRS Complex. Arch. Int. Med. 69: 437, 1942.

The syndrome of short P-R interval with a prolonged QRS complex is briefly reviewed, and two cases are reported.

An experimental study of cats and dogs showed that by the use of an abnormal electrical conducting pathway it was possible to produce electrocardiographic patterns closely resembling those occurring in human beings with the syndrome.

We feel the most logical explanation of this syndrome at present is a ventricular asynchronism, with premature contraction of one ventricle activated by an abnormal conducting pathway.

Further study, with a modification of the apparatus used, may be helpful in elucidating other problems in cardiac physiology.

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Geiger, A. J., Calabresi, M., and Blaney, L. F.: A Justification for the Increasing Use of Electrocardiography in Hospital Practice. Am. J. M. Sc. **203**: 219, 1942.

The increasing use of electrocardiography in local hospital practice appears justified. Requests for routine unnecessary electrocardiograms are decried, but their liberal use, if applied judiciously and intelligently, discloses abnormalities of clinical value sufficient to warrant the extra expenditure of laboratory service.

AUTHORS.

Klainer, M. J., and Altschule, M. D.: Prolongation of the P-R Interval in Patients With Paroxysmal Auricular Fibrillation and Flutter Following Myocardial Infarction. Am. J. M. Sc. **203**: 215, 1942.

The frequent occurrence of auricular fibrillation and flutter following cardiac infarction cannot be explained as directly due to anatomic findings, since the latter lesions are almost always ventricular.

Sixty-four per cent of patients with paroxysmal auricular fibrillation and flutter due to cardiac infarction also have a variable but abnormally prolonged P-R interval within a few days of the onset of fibrillation.

Available evidence, though scanty, suggests that the prolonged P-R interval of cardiac infarction is probably due to increased vagal activity.

Since increased vagal activity appears to be one factor responsible for the occurrence of auricular fibrillation in general, the occurrence of this arrhythmia following ventricular infarction becomes understandable.

AUTHORS.

Brody, H.: Drainage of the Pulmonary Veins Into the Right Side of the Heart. Arch. Path. **33**: 221, 1942.

Drainage of all or of part of the lungs into the major venous system is relatively uncommon. One hundred cases, of which thirty-five represent total drainage into the right atrium or its tributaries, have been collected from the literature. Two additional cases are described; in one the pulmonary veins drained into the coronary sinus, and in the other, into the superior vena cava. Of the thirty-seven patients with complete drainage into the right side of the heart or its tributaries, only eight lived beyond six months. In all cases in which the information is available, the foramen ovale was open. In about one-half, the ductus arteriosus was closed or almost closed. In the latter, all the blood reaching the systemic circulation passed through the aortic valve and, to reach the left side of the heart, passed through the foramen ovale. As the balance between the right and the left side of the heart in these cases had to be maintained through the foramen ovale and the ductus arteriosus, the gradual closing of these, particularly the latter, might have produced imbalance, with decompensation and death. In comparing cases in which there was partial or total drainage into the right side of the heart, it appears that, when less than 50 per cent of the pulmonary return is abnormally carried into the major venous circulation, there is little likelihood of decompensation, and such persons reach adult age.

The possible embryologic explanations of these cases are briefly discussed.

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Shillito, F. H., Chamberlain, F. L., and Levy, R. L.: Cardiac Infarction: The Incidence and Correlation of Various Signs, With Remarks on Prognosis. J. A. M. A. **118**: 779, 1942.

In the fifty cases of uncomplicated cardiac infarction an analysis was made of the incidence, time of appearance, and duration of certain signs.

Increase in the sedimentation rate of the erythrocytes was observed in all but one instance. Fever occurred invariably. Other signs were less frequently present.

A rectal temperature above 104° F., a leucocyte count higher than 25,000 or a venous pressure over 200 mm. of water indicated a grave prognosis. Seven of the eight patients showing any one of these signs died within sixteen days after the coronary attack.

The level of the sedimentation rate is helpful in the differentiation between anginal pain and cardiac infarction. It is of particular value in cases of infarction with mild symptoms which are not seen by the physician during the first few days of illness. The degree of increase is not an index of the severity of the attack nor does it serve as a guide in prognosis.

AUTHORS.

Butterworth, J. S., and Poindexter, C. A.: The Formol-Gel Test in Rheumatic Fever. Am. J. M. Sc. **203**: 278, 1942.

The formol-gel test is essentially a test for hyperglobulinemia and has no correlation with the erythrocyte sedimentation rate.

It is of little or no value in the diagnosis of acute rheumatic fever with or without carditis.

AUTHORS.

Ash, R.: Cardiac Signs in Rheumatic Infection of Childhood. Am. J. Dis. Child. **63**: 1, 1942.

The cardiac findings in a group of 553 rheumatic children who had been observed over an average period of 9.6 years following the primary infection are described.

Thirty-eight per cent of the group presented no definite clinical evidence of heart disease during the initial illness. Signs of valvular deformity made their appearance subsequently in 19 per cent of these children, associated with acute recrudescences of rheumatic infection in 80 per cent of the cases.

There were 340 children in whom a diagnosis of heart disease had been made following onset of the infection. Regression of cardiac signs occurred in 10 per cent.

A mid-diastolic blow heard to the right of the apex in association with a systolic murmur tended to appear early in the course of acute carditis (at a time when the mitral valve is dilated rather than stenosed) and to disappear with subsidence of the infection. It would seem to be an indicator of active infection rather than a guide to the presence of a narrowed valve. An additional clue to the existence of active carditis was the presence of a high-pitched musical screech heard as a component of the systolic murmur in the region of the apex.

The diastolic thrill and rumble of the adult type of mitral stenosis had developed in somewhat less than 10 per cent of the cases, the average delay of appearance having been five years following onset of rheumatic infection.

The outcome of the disease was influenced by the type of onset, acute carditis presenting the most ominous prognosis, and chorea, the most favorable. Chorea was most common as an initial manifestation among persons who developed mitral stenosis and least common among those who developed aortic insufficiency.

Acute pericarditis was associated with the highest death rate, followed in order of severity by aortic and mitral disease and by combined mitral insufficiency with stenosis. The death rate was relatively low among those with pure mitral stenosis.

At the end of the period of observation one-fourth of the children had died of heart disease, a third of these deaths having occurred within the first year of infection. Sixty per cent of the group either had no heart disease or were not prevented by their cardiac damage from leading a normal existence.

AUTHOR.

Irving, L., Scholander, P. F., and Grinnell, S. W.: The Regulation of Arterial Blood Pressure in the Seal During Diving. Am. J. Physiol. 135: 557, 1942.

Although the heart of the seal slows during diving below 10 per cent of the resting frequency, electrocardiograms showed little change in individual heart beats. The pressure in the femoral artery remained at the normal level in spite of the bradycardia. An example of peripheral vasoconstriction is shown in the closure of an artery of the toe during the dive. This arterial constriction is apparently under reflex control and may be set in operation by many stimuli bearing no relation to respiration. Observed contraction of mesenterial vessels showed that there is a considerable reduction of their circulation during diving. These examples of peripheral vasoconstriction during diving along with others that are known indicate vascular adjustments which serve to maintain a normal arterial pressure which could maintain the circulation of a few tissues like the brain in spite of the extreme bradycardia.

AUTHORS.

Young, Richard H.: Association of Postural Hypotension With Sympathetic Nervous System Dysfunction; Case Report, With Review of Neurologic Features Associated With Postural Hypotension. Ann. Int. Med. 15: 910, 1941.

A review of the literature reveals that neurologic features are quite common in cases of postural hypotension. In recent years there has been an increasing interest in the possibility that postural hypotension is a manifestation of dysfunction of the sympathetic nervous system.

A case is reported which shows clinical features of a bradykinetic type of Parkinsonian syndrome associated with marked postural hypotension and other manifestations of sympathetic nervous system dysfunction.

As a result of pharmacologic experience in this case, it is suggested that the best method of therapy is one which produces sympathetic stimulation with ephedrine or benzedrine, and parasympathetic inhibition by drugs of the atropine group.

AUTHOR.

Luke, J. C.: The Diagnosis of Chronic Enlargement of the Leg. Surg., Gynec. & Obst. 7: 472, 1941.

This presentation is an attempt to organize the scattered information on the subject of the unilateral, chronic, enlarged leg so as to present a guide in its diagnosis. The subject of treatment has been excluded.

Six main groups are described, each different from the standpoint of etiology. They are: congenital hypertrophy; lymphatic stasis and obstruction, both congenital and acquired; developmental venous retardation; mixed lymphatic and venous partial obstruction; congenital arteriovenous fistulas; and miscellaneous.

Group three, that of developmental venous retardation, is presented, as far as can be discovered, for the first time and a case history is given in detail.

AUTHOR.

Antoni, Nils: Buerger's Disease, Thrombo-Angiitis Obliterans, in the Brain. Report of Three (Four) Cases. Acta med. Scandinav. **108**: 502, 1941.

To summarize, it may be said that cerebral forms or cases of Buerger's disease are certainly not extremely rare; many patients thought to have juvenile arteriosclerosis probably suffer from this condition. One has to think of this possibility when confronted with cerebral disease in a young person, especially if the attacks are many and fleeting, and if one and the same focal sign disappears and recurs, maybe several times, perhaps to stay in the end. A combination of peripheral and central angiopathy should give special reason for suspicion. Intermittent claudication coupled with repeated cerebral insults, and perhaps cardiac disorder, should always lead to suspicions of Buerger's disease.

Unfortunately, there is not much to say about the therapy. Extirpation of the cervical ganglions and periarterial sympathectomy led to improvement in four cases from the Foerster clinic. A collection of 948 cases from the Mayo clinic in 1938 reveals, among other things, that sympathectomy does not cure the disease. If the thrombosis is primary to a certain extent, as it appears to be from the histologic picture in particular, the effects of heparin treatment should be tested. Perhaps the whole disease is a form of hypo-heparinemia.

AUTHOR.

Altschule, M. D., Linenthal, H., and Zamcheck, N.: Lung Volume and Pulmonary Dynamics in Raynaud's Disease. Effect of Exposure to Cold. Proc. Soc. Exper. Biol. & Med. **48**: 503, 1941.

Three patients suffering from Raynaud's disease were studied as to whether their lung volume and pulmonary dynamics were abnormal and whether exposure to cold affects their pulmonary function. Abnormalities in lung volume and pulmonary dynamics were noted only in the patient with diffuse pulmonary fibrosis. Exposure to cold caused no change in lung volume or its subdivisions in any of the patients. This indicates that the blood vessels of the lungs do not react in a manner similar to those of the hand and feet. This conclusion was strengthened by the observation that exposure to cold did not result in a change in the circulation time through the lungs.

VANDELLEN.

Davies-Colley, R.: Cirsoid Aneurysm. Guy's Hosp. Rep. **90**: 134, 1941.

Six cases of cirsoid aneurysm are described with the treatment.

All cirsoid aneurysms are the result of a developmental defect in the formation of the capillary barrier between the arteries and the veins. The majority follow an intermediate stage of visible dilatation of the capillaries, the cavernous angioma. Trauma may play the part of an accessory factor in their formation but is never the sole cause.

AUTHOR.

Cohen, S. M.: Traumatic Arterial Spasm. Guy's Hosp. Rep. **90**: 201, 1941.

Arterial spasm is discussed, and the literature is reviewed. Arterial spasm is shown to be a real clinical entity of special importance in time of war.

Special features discussed are the absent pulse, the duration of the spasm, pain or its absence, the use of tourniquets, and the relation of fracture and arterial damage. A number of cases are recorded to illustrate these features.

It is stressed that the use of violent traction methods may precipitate arterial spasm and that, especially in time of war with the ever lurking danger of gas-

gangrene infection, complete reduction may often be postponed for a few days with greater safety. The phenomenon of arterial spasm is critically examined, and it is recognized that much of it still requires explanation. The general features and rationale of the treatment of the jeopardized limb are discussed.

AUTHOR.

Hailey, H. R.: Popliteal Aneurysm. Guy's Hosp. Rep. **90**: 255, 1941.

Thirty-five cases of popliteal aneurysm are reviewed. The etiology of the condition is discussed, and the importance of trauma is stressed. Syphilis does not appear to be an important cause.

The relative frequency of the symptoms and signs are analyzed. A swelling exhibiting expansile pulsation in the popliteal fossa of a young or middle-aged man of arduous occupation and intemperate habits and associated with pain in the knee or calf, and sometimes also with features of arterial occlusion forms the typical clinical picture.

The only common complication is rupture which is frequently spontaneous, and often followed by gangrene.

The various forms of treatment are detailed. Excision of the sac is advised as the method of choice in those cases in which it is technically possible.

The rarity of gangrene following operations for popliteal aneurysm is commented upon. This is apparently due to the formation of an adequate collateral circulation in most cases before operation.

In spite of this the importance of determining the efficiency of the collateral circulation before operation is emphasized. This may be done by the reflex vasodilatation test, the reactive hyperemia test, by arteriography using uroselectan, and not thorotrast which is dangerous, or by watching the effects of temporary occlusion of the main artery by a Crile's clamp.

AUTHOR.

Welch, C. E., and Faxon, H. H.: Thrombophlebitis and Pulmonary Embolism. J. A. M. A. **117**: 1502, 1941.

It is only fair to state that the operation of ligation of the femoral vein has appealed to us more strongly as we have become more familiar with the procedure. At present, we believe that the immediate decision to be made in any given case of thrombophlebitis is whether the patient should be treated conservatively or by ligation of the vein. If conservative therapy is employed, lumbar injection of procaine hydrochloride should be done if vasospasm is considerable. If the deep venous channels are interrupted, heparin is often of value administered postoperatively. It must be emphasized that these concepts may be modified greatly as our experience increases. The important fact is that thrombophlebitis is no longer observed passively but is now accepted as a disease that must be vigorously treated.

AUTHORS.

Pelner, L., and Cohn, I. Primary Thrombosis of the Axillary and Subclavian Vein. Am. J. M. Sc. **203**: 340, 1942.

The literature concerning primary or effort thrombosis of the axillary and subclavian veins has been reviewed. Three personally observed cases, two of which were accompanied by venography, were described. The possible causes of this condition were evaluated.

Two of our patients could not recall any injury immediately preceding the onset of the condition, but did give a history of injury some time before the thrombosis.

AUTHORS.

Fahr, G., and Ershler, I.: Studies of the Factors Concerned in Edema Formation. II. The Hydrostatic Pressure in the Capillaries During Edema Formation in Right Heart Failure. Ann. Int. Med. 15: 798, 1941.

The cause of edema formation in right heart failure is the rise in capillary hydrostatic pressure. Anoxemia probably plays no essential part in edema formation in right heart failure.

A tendency to edema formation develops when the hydrostatic pressure in the venous end of the capillaries rises to within 2 mm. or less of the colloid osmotic pressure. If the patient is up and about, if no precautions are taken as to salt and water restriction, and if no diuretics are given, edema will develop.

If the colloid osmotic pressure is the normal of 22 mm. Hg, edema tendency is present if the hydrostatic pressure in the venous end of the capillary is 20 mm. Hg or the venous pressure in the arm vein is 13 mm. Hg or 17 cm. H_2O.

A drop in colloid osmotic pressure of 7 mm. Hg or a rise in capillary pressure of 8 mm. Hg produces approximately the same edema tendency.

Edema tendency is present when the colloid osmotic pressure is not more than 9 mm. Hg higher than the venous pressure in the arm.

AUTHORS.

Stead, E. A., Jr., and Ebert, R. V.: Shock Syndrome Produced by Failure of the Heart. Arch. Int. Med. 69: 369, 1942.

A clinical picture which is similar in certain respects to that observed in surgical shock or hemorrhage is sometimes seen in patients with chronic congestive failure or with acute myocardial infarction. The patients present signs of a decreased peripheral blood flow with diminished or no radial pulse, cold extremities, narrowed pulse pressure and a relatively well-maintained diastolic pressure.

The patients with a previous history of congestive failure had an elevated systemic venous pressure. The patients with acute myocardial infarction without previous congestive failure had a normal systemic venous pressure but exhibited marked pulmonary congestion and edema.

There was evidence of slight hemoconcentration in the patients with acute myocardial infarction. This may be due to loss of fluid into the lungs.

Because of the simultaneous presence of evidence of diminished peripheral blood flow and evidence of congestion either of the pulmonary or of the systemic venous bed, it is thought that the clinical picture is produced by failure of the heart, rather than by an inadequate venous return due to a decrease in blood volume or to peripheral pooling of blood.

The terms peripheral circulatory failure and shock should not be applied to the signs of a decreased cardiac output due to heart failure. They should be restricted to those conditions in which the cardiac output is diminished because of an inadequate venous return.

AUTHORS.

Abramson, D. I., and Fierst, S. M.: Resting Peripheral Blood Flow in the Hyperthyroid State. Arch. Int. Med. 69: 409, 1942.

The rate of blood flow through the hand, forearm and leg was studied in a series of twelve hyperthyroid subjects by means of the venous occlusion plethysmographic method. In seven of the patients opportunity was offered to observe the changes in flow for some time after thyroidectomy.

The average resting blood flow in the forearm and leg of the hyperthyroid subjects was significantly increased over that of a control series. After thyroidectomy there was a decrease, with a return to a normal level in eleven to sixty-three days after operation.

The average resting blood flow in the hand was not strikingly increased, although some of the individual readings were significantly greater than those of the control group. After thyroidectomy in the majority of the cases the flow decreased to a subnormal level.

The rate of fall in peripheral blood flow to normal levels, subsequent to operation, occurred more slowly than did the decrease in pulse rate and pulse pressure.

AUTHORS.

Warren, M. F., and Drinker, C. K.: The Flow of Lymph From the Lungs of the Dog. Am. J. Physiol. 136: 207, 1942.

A method for collecting lymph from the lungs of the dog is described. The experiment requires opening the chest to expose the anterior mediastinum and artificial respiration is used during its course.

The composition of lung lymph resembles that of cardiac lymph. In eighteen dogs the average protein content was 3.66 per cent.

When artificial respiration is unduly great or when the lungs are quiescent, lymph flow is greatly reduced.

Ventilation with a mixture low in oxygen invariably increases lymph flow. If pressure in the pulmonary veins is heightened, lymph flow is greatly augmented and the lymph soon resembles blood.

The drainage of lymph from both lungs is in the main via the right lymphatic duct, comparatively little lung lymph being delivered to the circulation by the thoracic duct.

AUTHORS.

Sanches-Perez, J. M.: Cerebral Angiography. Surgery 10: 535, 1941.

A complete cerebral angiographic exploration can establish in many cases an exact diagnosis of a lesion which is impossible to define and to localize by other means of exploration, as in cerebral aneurysm or angioma. The author uses thorotrast and describes the technique. He states that the procedure is harmless to the patient.

NAIDE.

Gross, S. W.: Cerebral Arteriography With Diodrast, Fifty Per Cent. Radiography 37: 487, 1941.

The injection of 50 per cent diodrast into the common carotid artery uniformly resulted in good visualization of the cerebral circulation. The technique of administration is fully described.

NAIDE.

Clagett, A. H., Jr.: Cardiac Roentgenology: The Value of Exact Cardiac Measurements. Am. J. Roentgenol. 46: 794, 1941.

As a whole, the cardiothoracic ratio is unreliable as an index of cardiac abnormality. It is felt that too much stress is being placed upon cardiac measurements, especially the cardiothoracic ratio. The greatest amount of information obtainable from the roentgenologic study of the heart is the configuration of the

cardiac silhouette. This is best obtained by a careful roentgenoscopic study with visualization of the esophagus followed by an orthodiogram or a teleroentgenogram. As such, and used only as an adjunct to clinical methods, the roentgen ray can be of great value in the diagnosis of heart disease.

AUTHOR.

Brock, R. C.: Brachial Artery Embolectomy. Report of an Unusual Case. Guy's Hosp. Rep. 90: 230, 1941.

A case is reported in which six (possibly seven) embolisms had occurred over a period of eight years in a man suffering from auricular fibrillation and mitral stenosis.

These emboli had led to a right hemiplegia with aphasia, gangrene of the right leg necessitating amputation, and ischemic necrosis of the left anterior tibial muscles causing paralysis and deformity of the left leg. His only remaining useful limb, the left arm, was threatened by a seventh embolus which lodged in the left brachial artery. Operation was performed some seven hours after embolism, and the artery was repaired by suture after removal of the embolus. Immediate and dramatic restoration of the circulation in the limb followed. Convalescence was uneventful.

AUTHOR.

Spalding, J. E.: Periarteritis Nodosa and Its Surgical Significance. Report of a Case. Guy's Hosp. Rep. 90: 234, 1941.

A case of periarteritis nodosa simulating chronic cholecystitis with gallstones is described. The diagnosis was made by histologic examination of the organ. After operation, general symptoms of the disease appeared.

Although periarteritis nodosa is a nonsurgical condition, it is of interest to the surgeon because of its occasional close mimicry of acute or subacute surgical diseases, more especially of the abdomen. Sometimes a true surgical emergency may be caused by it.

The full clinical picture is outlined, in the polysymptomatic cases the correct diagnosis should be made, but when the first symptoms suggest an abdominal emergency (such as acute appendicitis, simulated by a hematoma) a correct clinical diagnosis may be impossible. In such cases histologic examination may indicate the correct diagnosis.

AUTHOR.

Woods, W. W., and Peet, M. M.: The Surgical Treatment of Hypertension. II. Comparison of Mortality Following Operation With That of the Wagener-Keith Medically Treated Control Series: a Study of Seventy-Six Cases From Five to Seven Years After Operation. J. A. M. A. 117: 1508, 1941.

The prognosis of patients with a high level of blood pressure and angiospastic changes of the retinal arterioles is much more favorable following operation than following medical treatment.

The surgical treatment of patients with malignant hypertension has resulted in a survival of 33 per cent after five years, whereas following medical treatment in the control series the mortality was more than 99 per cent.

In general, a favorable prognosis following operation seems to depend on a minimal degree of retinal arteriolar sclerosis rather than on the level of blood pressure, or the absence of retinitis with hemorrhages and exudates, or papilledema.

AUTHORS.

Jensen, H., Corwin, W. C., Tolksdorf, S., Casey, J. J., and Bamman, F.: Reduction of Arterial Blood Pressure of Hypertensive Rats by Administration of Renal Extracts. J. Pharmacol. & Exper. Therap. **73**: 38, 1941.

A method is described for the preparation of renal extracts which are capable of reducing the blood pressure of rats with experimental hypertension. A total dose of 58 Gm. equivalent of fresh hog kidney, injected intramuscularly twice daily for a period of four days, was found to produce a pronounced and prolonged lowering of the blood pressure.

Oral administration of similar renal extracts at comparatively high doses failed to produce a comparable effect on the blood pressure.

Extracts of beef liver and muscle prepared according to the same procedure as employed for renal extracts failed to lower the blood pressure in hypertensive rats.

The failure of hog renin to produce a lowering of blood pressure in hypertensive rats in our routine four-day test seems to militate against the interpretation that the antipressor effect of renal extracts might be due to the formation of an antirenin substance.

AUTHORS.

Mudd, S., and Flosdorf, E. W.: Blood and Blood Substitutes in the Treatment of Hemorrhage, Secondary Shock and Burns. New England J. Med. **225**: 868, 1941.

The role of blood and blood substitutes in the treatment of hemorrhage, secondary shock, and burns is briefly discussed.

Human plasma and serum are the most effective agents for restoring the volume of circulating fluid to normal in cases of shock and burns, as well as of hemorrhage in the absence of excessive bleeding.

Although serum and plasma are most easily and economically preserved in the liquid form, drying from the frozen state by the lyophile, cryochem and desivac processes is recommended for war purposes and under conditions requiring prolonged storage or transportation.

AUTHORS.

Barondes, R. deR.: Night Blindness: Its Treatment With Vasodilating Drugs. M. Rec. **154**: 427, 1941.

When the retinal arteries, arterioles and capillaries become spastic, or mildly sclerosed as a result of disturbances of innervation, etc., the vessels are unable to deliver the amount of blood to the nerve endings in the light-perceiving layer of the retina. Consequently a state of nutritional increase of visual purple arises in these parts, and the metabolic increase of visual purple cannot take place. Without ample regeneration, a depletion of this night-seeing agent results, and the reaction to faint illumination, as in darkness, becomes very poor.

The administration of vasodilating drugs markedly increased the eyes' sensitivity to faint light. The drugs which can accomplish this are nitroglycerine, thiocyanates, strychnine, hexanitrate, erythrol nitrate, and erythrol succinate. However, in advanced arteriosclerosis little vasodilatation can be expected.

AUTHOR.

Book Review

LA ENFERMEDAD REUMATICA: By Domingo Urrutia M., Jefe de Clinica Médica, and Samuel Vaisman B., Ayudante de Clinica Médica, Universidad de Chile. Imprenta "La Sud-America," Santiago de Chile, 1941, 191 pages, 22 illustrations.

This is a report which was presented at an annual meeting of the Medical Society of Santiago.

After a chapter on the social importance of rheumatic infection, the authors discuss the etiology and pathogenesis of the disease. The infectious theories are reviewed, and the allergic theory is emphasized. Predisposing causes, such as heredity, sex, climate, and focal infection, are considered. The value of tonsillectomy is underestimated in the prevention of rheumatic fever. The authors admit that the cause of the disease is still unknown, and that the observed lesions are the result of sensitization to different bacterial proteins, especially from bacteria which produce acute inflammation of the throat (among which the *Streptococcus hemolyticus* is the most important). No mention is made of the possibility that a filterable virus may be the etiologic agent, in spite of the fact that valuable evidence has recently been obtained to suggest it.

Inasmuch as the pathologic changes take place in the mesenchymal tissues, typical lesions may occur in any organ. They consist of the following, in the order given: (a) exudative-degenerative changes which terminate in necrosis of the collagenous bundles, (b) proliferative changes which lead to the formation of the specific gigantocellular granuloma (Aschoff nodule), and (c) scarring of the lesions. In the heart the characteristic location of the lesions is the posterior wall of the left ventricle and the septum. The myocardial involvement is the most important, and, according to the authors, pericardial and endocardial lesions play only a secondary role in causing heart failure and death.

Rheumatic infection is regarded as a chronic disease, with acute, recurrent attacks. The myocardial lesion is constant, especially in young people. The other manifestations (polyarthritis, chorea) are said to be important only for diagnostic purposes.

The extent and severity of the myocarditis are related to the age of the patient at the time of onset of the disease, and to the duration and number of recurrences. The intensity of the myocarditis and the tendency to recurrence are inversely proportional to the age of the patient.

Sedimentation rate, roentgenologic examination, and the electrocardiogram are discussed. The prolongation of the P-R interval and the A-V block which are so commonly encountered are attributed to edema of the bundle of His and increased excitability of the vagus.

Sodium salicylate and aminopyrine are regarded as useful in the treatment of the joint manifestations, but have no effect on the cardiac involvement. These drugs are said to be antiexudative and antiallergic.

The prophylaxis of the disease is discussed.

ALDO LUISADA.

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